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(54) Title: SELECTIVE NPY (Y5) ANTAGONISTS

(57) Abstract: This invention is directed to bicyclic and tricyclic compounds which are selective antagonists for NPY (Y5) recep-
tors. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the
invention and a pharmaceutically acceptable carrier. This invention provides a pharmaceutical composition made by combining a
therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier. The invention provides
a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of the
invention and a pharmaceutically acceptable carrier. This invention further provides the use of a compound of the invention for the
preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the
activity of a human Y5 receptor.



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SELECTIVE NPY (Y5) ANTAGONISTS5 Background Of The Invention

This application claims priority of and is a continuation-in-part of U.S. Serial No. 09/343,635, filed June 30, 1999, U.S. Serial No. 09/343,633, filed June 30, 1999, and
10 U.S. Serial No. 09/343,993, filed June 30, 1999, the contents of all of which are hereby incorporated by reference into the subject application.

Throughout this application, various references are
15 referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be
20 found at the end of this application, preceding the claims.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family
25 with widespread distribution throughout the mammalian nervous system (Dumont et al., 1992). The family includes the pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and
30 NPY, synthesized primarily in neurons (Michel, 1991; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr³⁶ (or Y³⁶ in the single letter
35 code). The striking conservation of Y³⁶ has prompted the

reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt et al., 1987), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

5

NPY and its relatives elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". While the Y1, Y2, Y3, and Y4 (or PP) receptors were each described previously in both radioligand binding and functional assays, the "atypical Y1" receptor is unique in that its classification is based solely on feeding behavior induced by various peptides including NPY.

15

The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden et al., 1994). NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark et al., 1984; Levine and Morley, 1984; Stanley and Leibowitz, 1984). The stimulation of feeding behavior by NPY is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. For example, direct injection of NPY into the hypothalamus of satiated rats can increase food intake up to 10-fold over a 4-hour period (Stanley et al., 1992). Similar studies using other peptides has resulted in a pharmacologic profile for the "atypical Y1" receptor according to the rank order of potencies of peptides in stimulating feeding behavior as follows: NPY_{2-36} \sim NPY \sim PYY \sim $[\text{Leu}^{31}, \text{Pro}^{34}]\text{NPY}$ $>$ NPY_{13-36} (Kalra et al., 1991; Stanley et al., 1992). The profile is similar to that of

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a Y1-like receptor except for the anomalous ability of NPY₂₋₃₆ to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report in J. Med. Chem. by Balasubramaniam and co-workers (1994) showed that feeding can be regulated by [D-Trp³²]NPY. While this peptide was presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp³²]NPY on feeding. In contrast to other NPY receptor subtypes, the "feeding" receptor has never been characterized for peptide binding affinity in radioligand binding assays.

This problem has been addressed by cloning rat and human cDNAs which encode a single receptor protein, referred to herein as Y5, whose pharmacologic profile links it to the "atypical Y1" receptor. The identification and characterization of a single molecular entity which explains the "atypical Y1" receptor allows the design of selective drugs which modulate feeding behavior (WO 96/16542). It is important to note, though, that any credible means of studying or modifying NPY-dependent feeding behavior must necessarily be highly selective, as NPY interacts with multiple receptor subtypes, as noted above (Dumont et al., 1992).

As used in this invention, the term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific but by no means limiting examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization,

ion channel activation, guanylate cyclase, and inositol phospholipid hydrolysis. Conversely, the term "agonist" refers to a compound which binds to, and increases the activity of, a receptor as compared with the activity of the receptor in the absence of any agonist.

In order to test compounds for selective binding to the human Y5 receptor the cloned cDNAs encoding both the human and rat Y2 and Y4 (or PP) receptors have been used. The human and rat Y5 receptors are described in coassigned U.S. Patent No. 5,602,024 and in PCT International Application PCT/US95/15646, published June 6, 1996, as WO 96/16542, the contents of which are hereby incorporated by reference into this application. The human and rat Y2 receptors are described in coassigned U.S. Patent No. 5,545,549 and in PCT International Application PCT/US95/01469, published August 10, 1995, as WO 95/21245, the contents of which are hereby incorporated by reference into this application. The human and rat Y4 receptors are described in coassigned U.S. Patent No. 5,516,653 and in PCT International Application PCT/US94/14436, published July 6, 1995, as WO 95/17906, the contents of which are hereby incorporated by reference into this application. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar et al., 1992; Herzog et al., 1992; Eva et al., 1990; Eva et al., 1992).

Using the NPY-Y5-selective antagonist CGP 71683A, it was demonstrated recently that food intake in free-feeding and energy-derived lean rats is mediated by the Y5 receptor (Criscione et al., 1998). CGP 71683A has high affinity for the cloned rat NPY-Y5 receptor subtype, but 1,000-fold lower affinity for the cloned rat NPY-Y1, Y2, and Y4

receptors. Examples of additional NPY-Y5-selective compounds are described in WO 97/20823, WO 98/35957, and WO 98/35944.

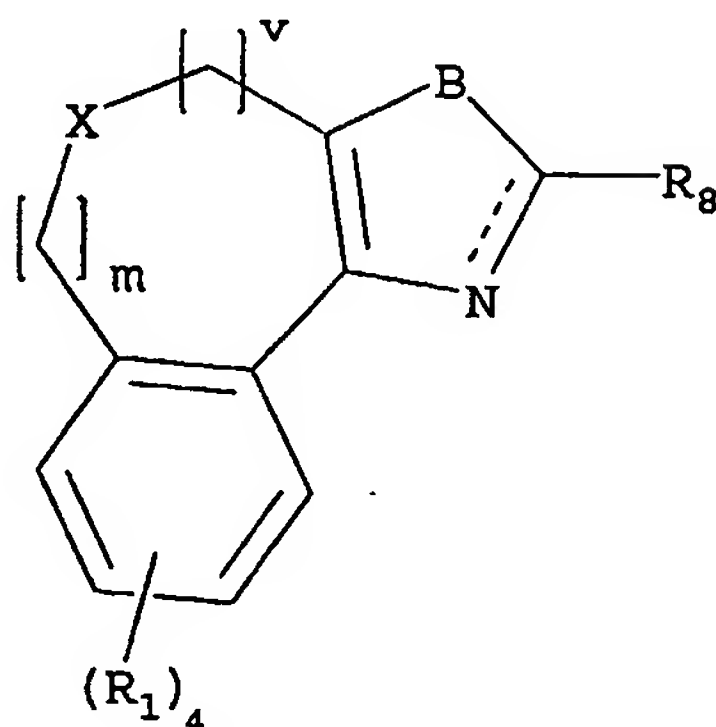
5 In different embodiments of this invention the synthesis of novel bicyclic compounds and tricyclic compounds which bind selectively to the cloned human Y5 receptor, compared to the other cloned human NPY receptors, and inhibit the activation of the cloned human Y5 receptor as measured in
10 in vitro assays is disclosed. The in vitro receptor binding and activation assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single Y-type receptor.

15

In addition, the compounds of the present invention may also be used to treat abnormal conditions such as feeding disorders (obesity and bulimia nervosa), sexual/reproductive disorders, depression, epileptic
20 seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleep disturbances, or any condition in which antagonism of a Y5 receptor may be beneficial.

Summary Of The InventionA. Tricyclic Compounds

5 This invention provides a compound having the structure:



10 wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

15 wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

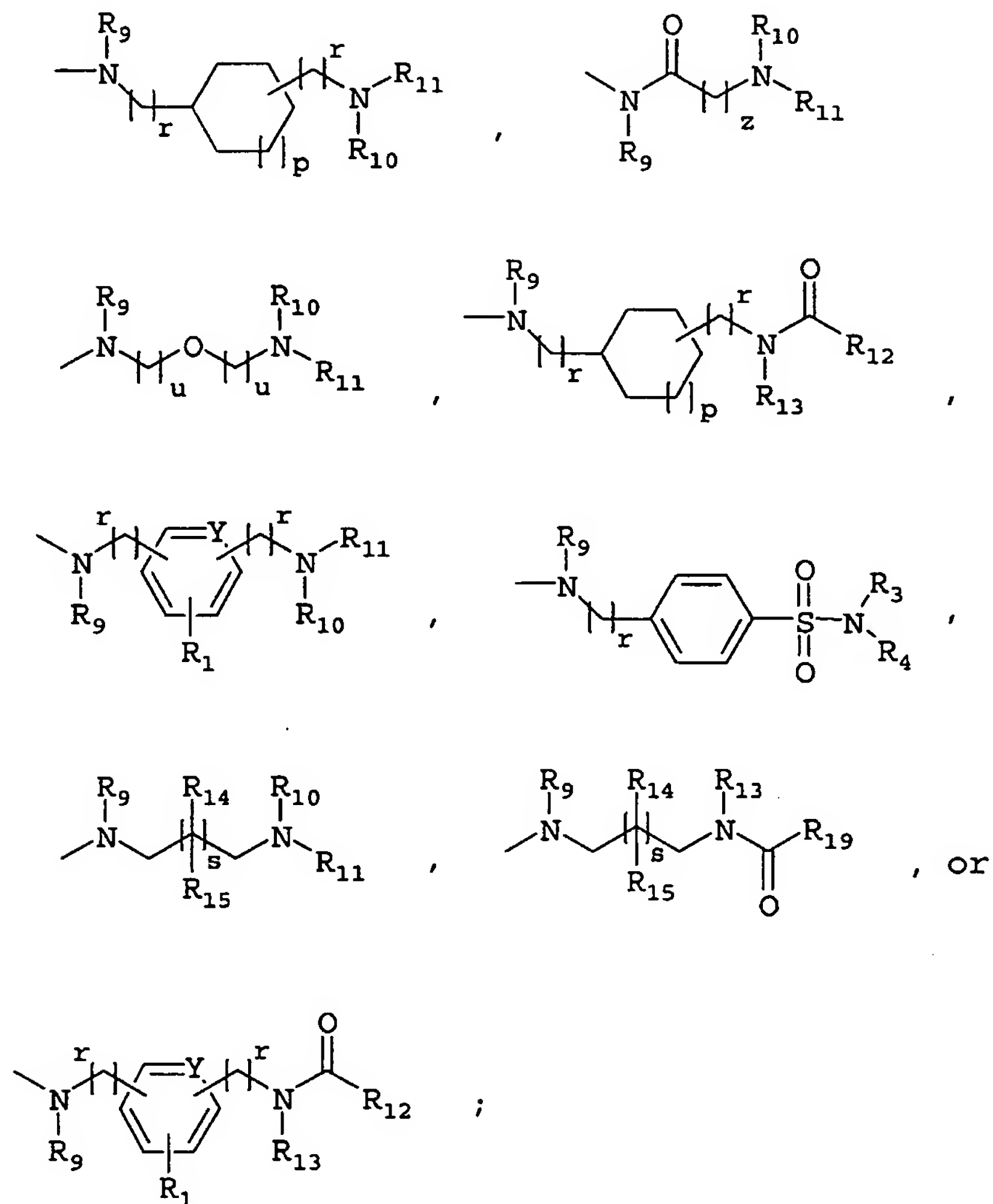
20 wherein B is O, NH or S;

wherein X is CHR₅, O or NR₅;

25 wherein each n independently is an integer from 0 to 6 inclusive;

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wherein R_8 is



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wherein Y is C or N;

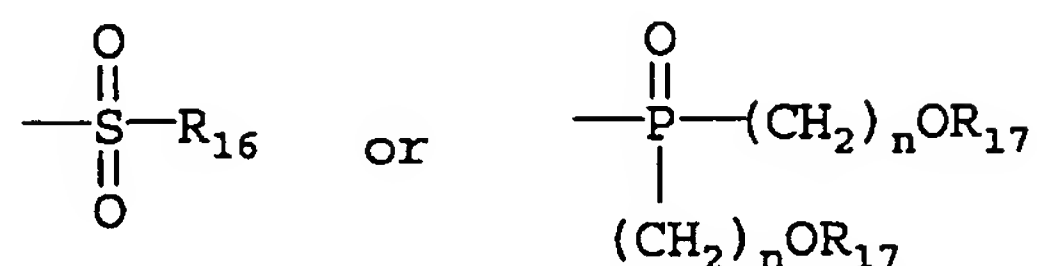
wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

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wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

8
 wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X is O, R_{12} cannot be methyl;

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl; provided that when X is O, R_{12} and R_{13} cannot be oxazolidinonyl;

9

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(CH_2)_rOR_5$;

5

wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is $-OH$, R_{15} cannot be F;

10

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more of F, Cl, $-CN$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$,

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perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be

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substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl,

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perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of

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F, Cl, Br, $-CN$, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

with the proviso that when X is O and R_8 is $NR_9(CH_2)_uO(CH_2)_uNR_{10}R_{11}$, R_{16} cannot be methyl;

5

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or
 10 branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$,
 15 $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

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wherein R_4 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or
 25 branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$,
 30 straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are 1-azetidiny1, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny1, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if -(CH₂)_nNR₅R₆, -(CH₂)_nOR₅, or -(CH₂)_nNR₅COR₅ are in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C₁-C₅ alkyl or (CH₂)_tOR₅; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with -(CH₂)_uOR₅; -COR₅; straight chained or branched C₁-C₅ alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -(CH₂)_nOR₅, straight chained or

branched C₁-C₃ alkyl,¹² perfluoroalkyl,
polyfluoroalkyl, or aminoalkyl;

5 wherein R₁₇ is H, straight chained or branched C₁-C₄ alkyl,
perfluoroalkyl, or polyfluoroalkyl;

wherein R₁₉ is (CH₂)_nOR₅, NR₅R₆, phenyl, or heteroaryl,
wherein the phenyl or heteroaryl may be substituted with
one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -
10 (CH₂)_nNR₅COR₅, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅,
-(CH₂)_nCONR₅R₆, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, ethylenedioxy,
methylenedioxy, straight chained or branched C₁-C₇ alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
15 cycloalkyl or cycloalkenyl;

wherein m is 0 or 1;

wherein each p independently is an integer from 0 to 2
20 inclusive;

wherein each r independently is an integer from 0 to 3
inclusive;

25 wherein each s independently is an integer from 1 to 6
inclusive;

wherein t is an integer from 1 to 4 inclusive;

30 wherein each u independently is an integer from 2 to 4
inclusive;

wherein v is 1 or 2;

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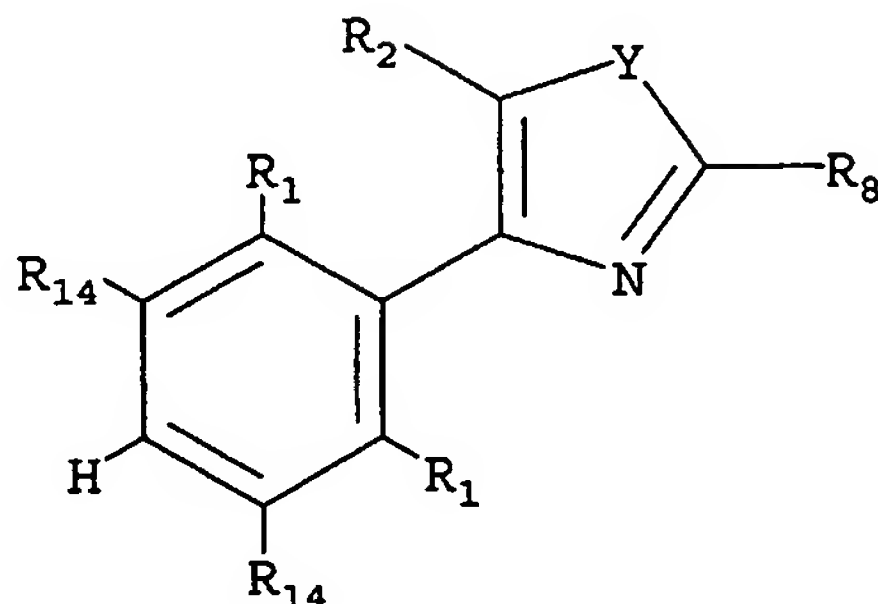
with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

5 or a pharmaceutically acceptable salt thereof.

B. Bicyclic Compounds

This invention provides a compound having the structure:



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wherein Y is O, S or NH;

wherein each R_{14} independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl; provided that if one R_{14} is phenyl, heteroaryl or C₁-C₇ phenylalkyl, the other R_{14} is H;

wherein each R_1 independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

wherein R_2 is H, straight chained or branched C_1 - C_4 alkyl,
 $-(CH_2)_tOR_5$, phenyl optionally substituted with one or more
 of F, Cl, Br, $-CF_3$, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$,
 5 $-(CH_2)_nOR_5$, or straight chained or branched C_1 - C_4 alkyl;

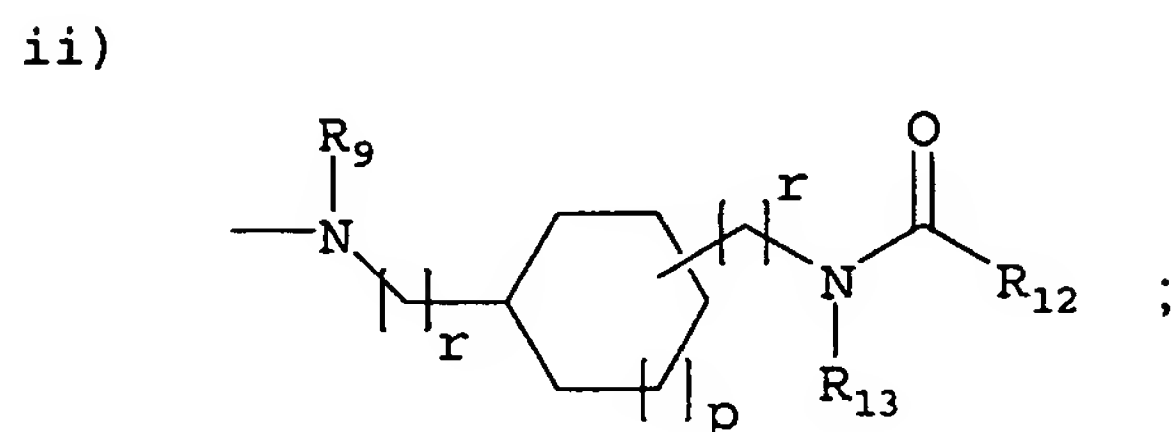
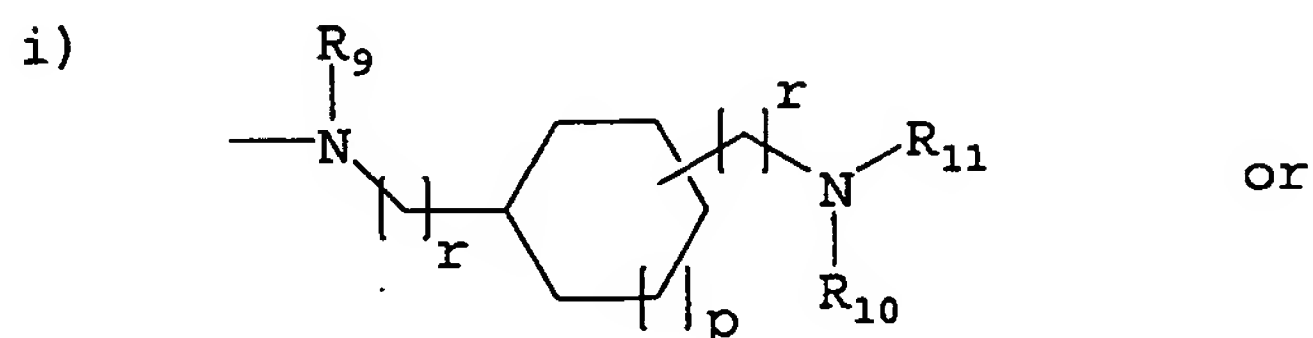
wherein R_5 is independently H; or straight chained or
 branched C_1 - C_7 alkyl;

10 wherein R_6 is independently H; or straight chained or
 branched C_1 - C_7 alkyl;

wherein each n independently is an integer from 0 to 6
 inclusive;

15

wherein R_8 is



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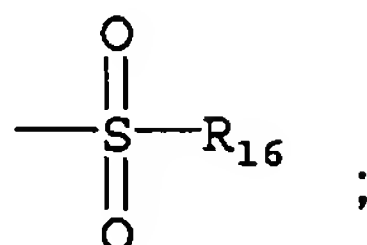
provided that R_1 or R_{14} cannot be $-OH$, when R_8 is (ii);

wherein R_9 is independently H; or straight chained or
 branched C_1 - C_4 alkyl;

25

wherein R_{10} is independently H ; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



wherein R_{12} is H , straight chained or branched C_1 - C_7 alkyl; or $(CH_2)_nOR_{17}$;

wherein R_{13} is independently $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl ; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F , Cl , $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, or straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may
 5 be substituted with one or more of F, Cl, -CN, - NR_5R_6 , - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nNR_5COR_5$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or
 10 cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; or phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5COR_5$, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 15 chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5COR_5$, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, or straight
 20 chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

wherein R_3 is independently H; - $(CH_2)_uOR_5$; -
 30 $(CH_2)_tCONR_5R_6$; - $(CH_2)_uNR_5COR_5$; - $(CH_2)_tCOR_7$; - $(CH_2)_tCO_2R_5$; - $(CH_2)_uNR_5R_6$; - $(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; or phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl;

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wherein the phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆,
 5 straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

10 wherein R₄ is independently H; -(CH₂)_uOR₅; -(CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -(CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or branched C₁-C₇ alkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 15 or phenyl or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆ phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl,
 20 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are 1-azetidiny, 1-pyrrolidiny, 1-piperidiny, or 1H-azepany, wherein the 1-azetidiny, 1-pyrrolidiny, 1-piperidiny, or 1H-azepany is substituted with one or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅,
 30 straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if -(CH₂)_nNR₅R₆, -(CH₂)_nOR₅, or -(CH₂)_nNR₅COR₅ are

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in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C₁-C₅ alkyl or (CH₂)_tOR₅; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with -(CH₂)_uOR₅; -COR₅; straight chained or branched C₁-C₅ alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -(CH₂)_nOR₅, straight chained or branched C₁-C₃ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

wherein R₁₇ is straight chained or branched C₁-C₄ alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein each p independently is an integer from 0 to 2 inclusive;

wherein each r independently is an integer from 0 to 3 inclusive;

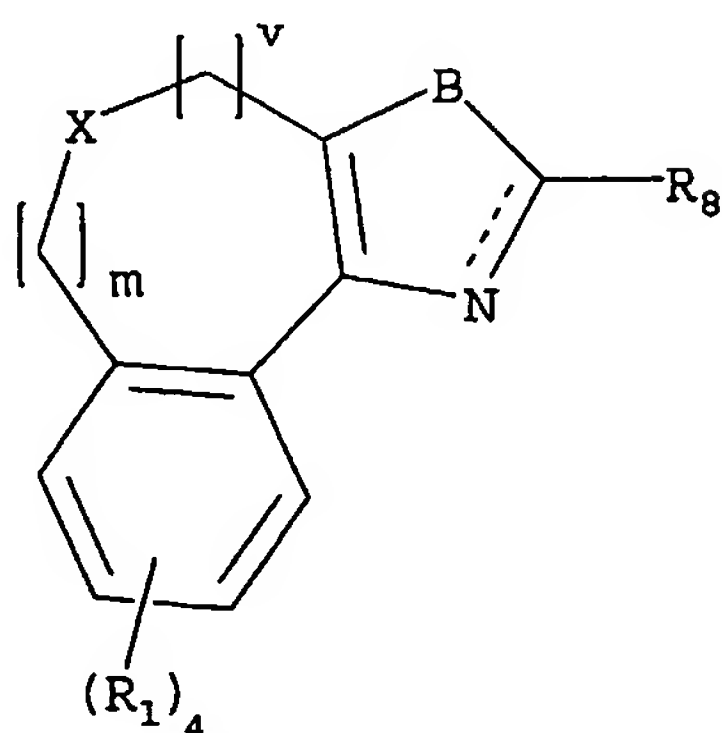
wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to 4 inclusive;

5 or a pharmaceutically acceptable salt thereof.

C. Tricyclic Compounds

The invention provides a compound having the structure:



5 wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

10 wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

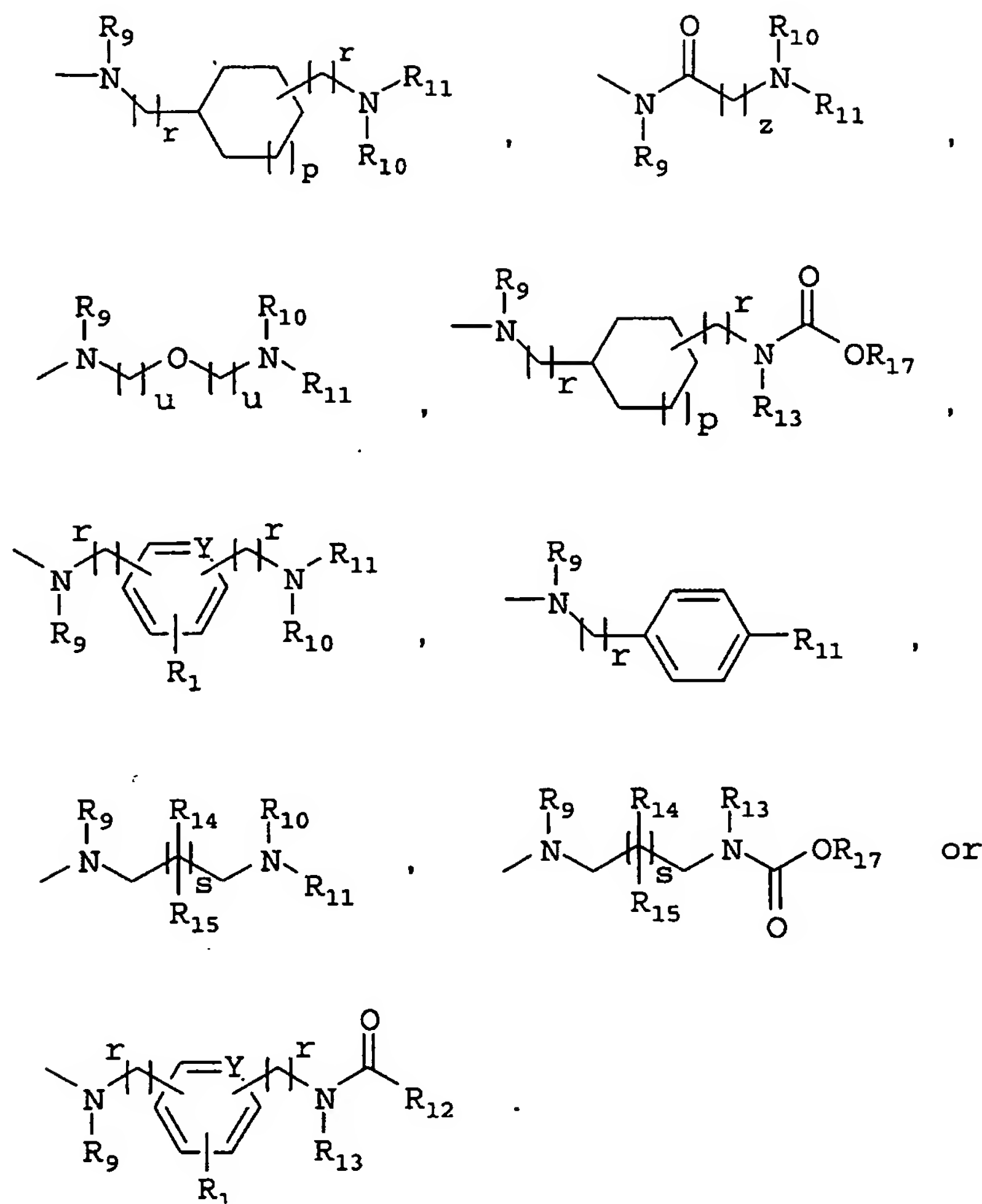
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wherein B is O, NH or S;

wherein X is S, SO or SO₂;

20 wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is



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wherein Y is C or N;

wherein R_7 is independently straight chained or branched
10 C_1 - C_7 alkyl;

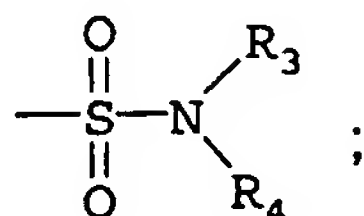
wherein R_9 is independently H; or straight chained or
branched C_1 - C_4 alkyl;

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wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is

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wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$;

10

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

30

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wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

5

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, C_1 - C_6 phenylalkyl or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

wherein R_4 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

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or R_3 and R_4 taken together with the nitrogen atom to which they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, $-(CH_2)_nNR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

20

or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C_1 - C_5 alkyl or $(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; $-COR_5$; $-CO_2R_5$; straight chained or branched C_1 - C_5 alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nOR_5$, straight chained or branched C_1 - C_3 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

30

wherein R_{17} is straight chained or branched C_1 - C_4 alkyl, perfluoroalkyl, or polyfluoroalkyl;

5 wherein m is 0 or 1;

wherein each p independently is an integer from 0 to 2 inclusive;

10 wherein each r independently is an integer from 0 to 3 inclusive;

wherein each s independently is an integer from 1 to 6 inclusive;

15

wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to 4 inclusive;

20

wherein v is 1 or 2;

with the proviso that when v is 2, m is 0;

25 wherein z is an integer from 2 to 7;

or a pharmaceutically acceptable salt thereof.

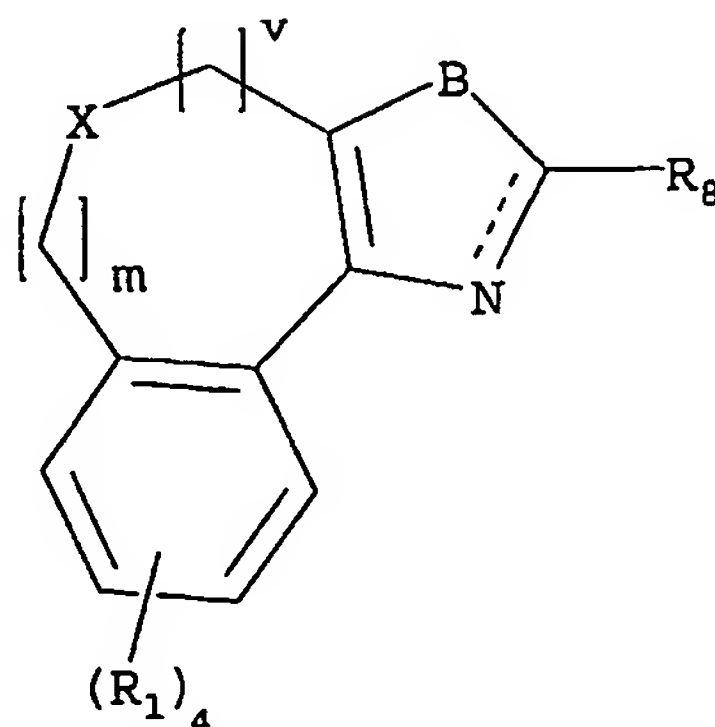
30 The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. This invention further provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this

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invention and a pharmaceutically acceptable
carrier. This invention further provides a process for
making a pharmaceutical composition comprising combining a
therapeutically effective amount of the compound of the
5 invention and a pharmaceutically acceptable carrier.

Detailed Description Of The InventionA. Tricyclic Compounds

This invention provides a compound having the structure:



wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

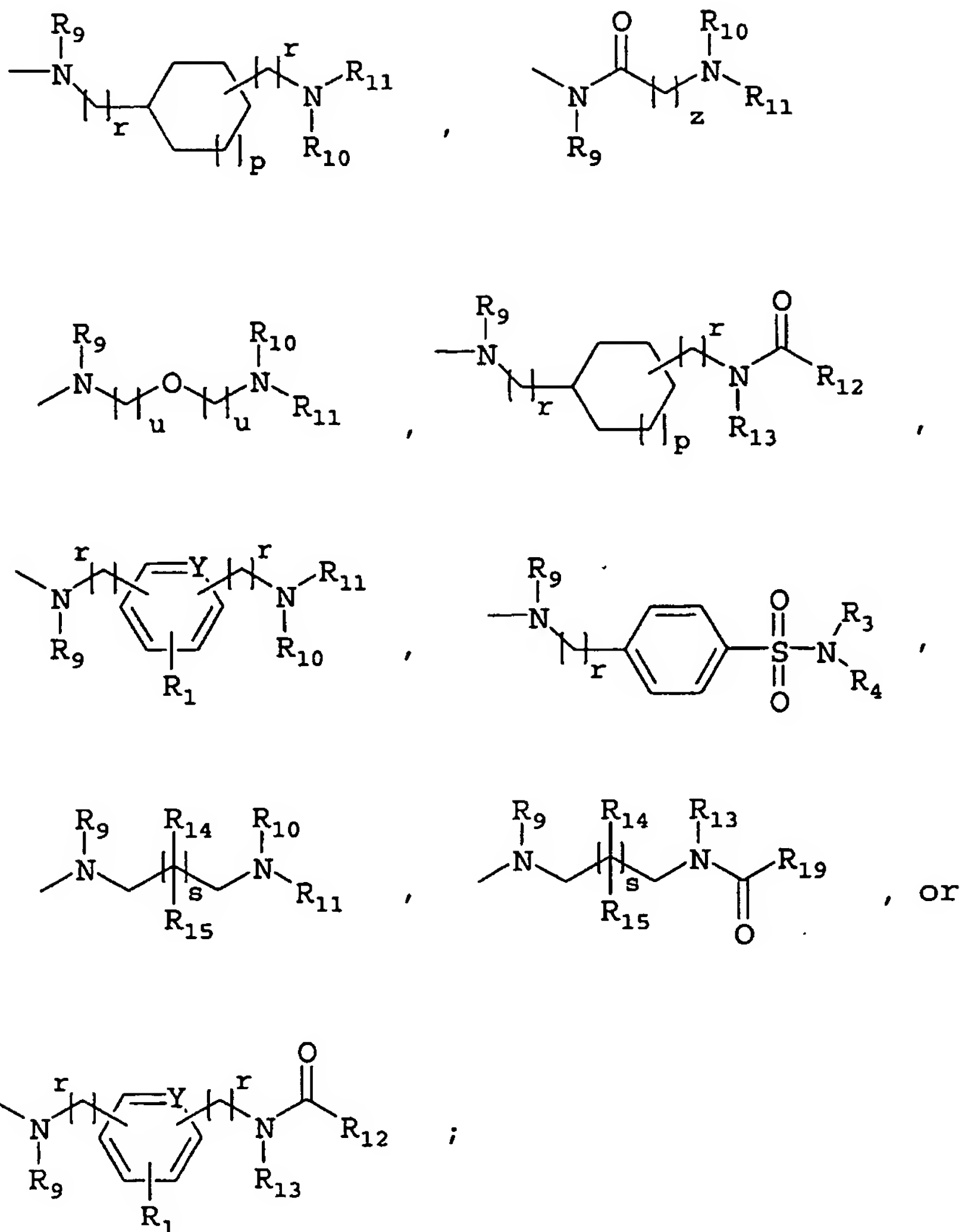
wherein B is O, NH or S;

wherein X is CHR₅, O or NR₅;

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is

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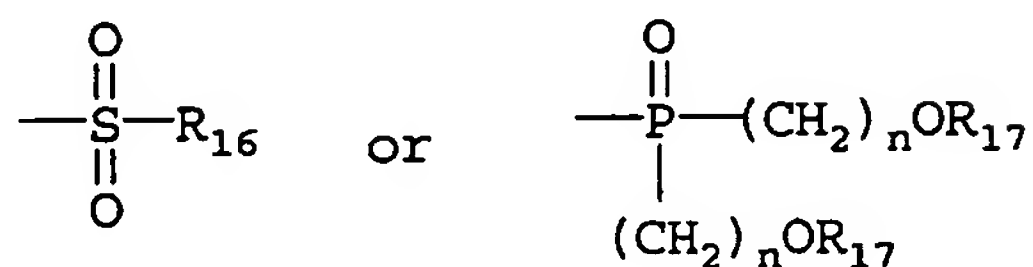
10 wherein Y is C or N;

wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

5 wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



10

wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X is O, R_{12} cannot be methyl;

15

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

30

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or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl; provided that when X is O, R_{12} and R_{13} cannot be oxazolidinonyl;

5

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(CH_2)_rOR_5$;

10

wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

15

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$,

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perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight

30 chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of

32

F, Cl, Br, -CN, -NO₂, -NR₅R₆, -
 (CH₂)_nNR₅COR₅, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -
 (CH₂)_nCONR₅R₆, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, ethylenedioxy,
 methylenedioxy, straight chained or branched C₁-C₇ alkyl,
 5 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

with the proviso that when X is O and R₈ is
 NR₉(CH₂)_uO(CH₂)_uNR₁₀R₁₁, R₁₆ cannot be methyl;
 10

wherein R₃ is independently H; -(CH₂)_uOR₅; -
 (CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 15 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl; wherein
 the phenyl, C₁-C₆ phenylalkyl or C₁-C₆ heteroarylalkyl may
 be substituted with one or more of F, Cl, Br, -CN, -NO₂,
 20 -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -
 (CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained
 or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl,
 or aminoalkyl, straight chained or branched C₂-C₇ alkenyl
 or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

25
 wherein R₄ is independently H; -(CH₂)_uOR₅; -
 (CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 30 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆
 phenylalkyl may be substituted with one or more of F, Cl,
 Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -

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(CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆,
 straight chained or branched C₁-C₇ alkyl, perfluoroalkyl,
 polyfluoroalkyl, or aminoalkyl, straight chained or
 branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or
 5 cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which
 they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-
 piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-
 10 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted
 with one or more of F, -CN, - (CH₂)_nNR₅R₆, -SO₂R₅, -
 (CH₂)_nCOR₇, - (CH₂)_nOR₅, - (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, -
 (CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 15 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 cycloalkyl or cycloalkenyl, or phenyl or heteroaryl;
 wherein if - (CH₂)_nNR₅R₆, - (CH₂)_nOR₅, or - (CH₂)_nNR₅COR₅ are
 in the 2-position, then n is not 0; wherein the phenyl or
 heteroaryl may be substituted with one or more of F, Cl,
 20 Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nCOR₇, -
 (CH₂)_nOR₅, - (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅, -
 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 25 cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which
 they are attached are morpholinyl, thiomorpholinyl,
 [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or
 30 [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl,
 [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or
 [1,4]diazepanyl is optionally substituted with straight
 chained or branched C₁-C₅ alkyl or (CH₂)_tOR₅; and wherein
 the nitrogen atom of the piperazinyl or [1,4]diazepanyl

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ring may be optionally substituted with -
(CH₂)_uOR₅; -COR₅; straight chained or branched C₁-C₅ alkyl;
or phenyl; wherein the phenyl may be substituted with one
or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, - (CH₂)_nOR₅, straight
5 chained or branched C₁-C₃ alkyl, perfluoroalkyl,
polyfluoroalkyl, or aminoalkyl;

wherein R₁₇ is H, straight chained or branched C₁-C₄ alkyl,
perfluoroalkyl, or polyfluoroalkyl;

10

wherein R₁₉ is (CH₂)_nOR₅, NR₅R₆, phenyl, or heteroaryl,
wherein the phenyl or heteroaryl may be substituted with
one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -
(CH₂)_nNR₅COR₅, -SO₂R₅, - (CH₂)_nCOR₇, - (CH₂)_nOR₅,
15 - (CH₂)_nCONR₅R₆, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, ethylenedioxy,
methylenedioxy, straight chained or branched C₁-C₇ alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
cycloalkyl or cycloalkenyl;

20

wherein m is 0 or 1;

wherein each p independently is an integer from 0 to 2
inclusive;

25

wherein each r independently is an integer from 0 to 3
inclusive;

wherein each s independently is an integer from 1 to 6
30 inclusive;

wherein t is an integer from 1 to 4 inclusive;

wherein each u independently ³⁵ is an integer from 2 to 4 inclusive;

wherein v is 1 or 2;

5

with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

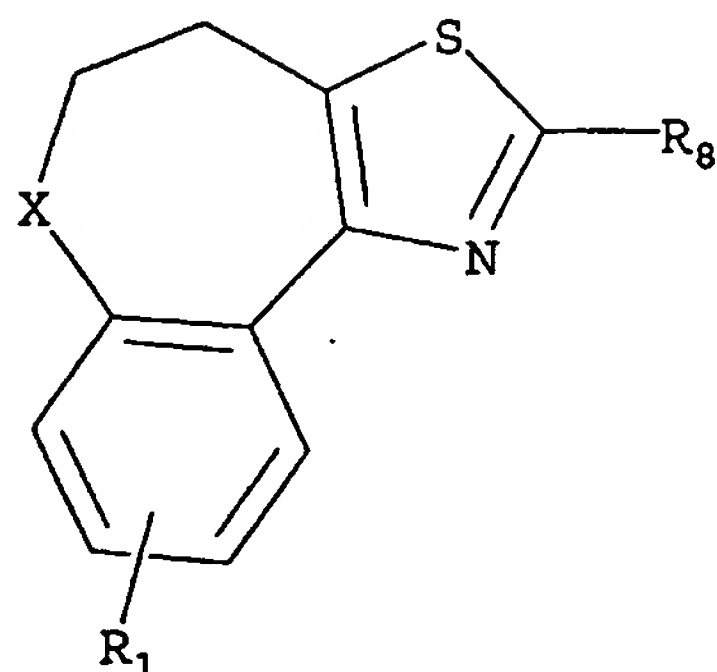
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or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound comprises the (+) enantiomer. In another embodiment, the compound comprises the (-) enantiomer.

15

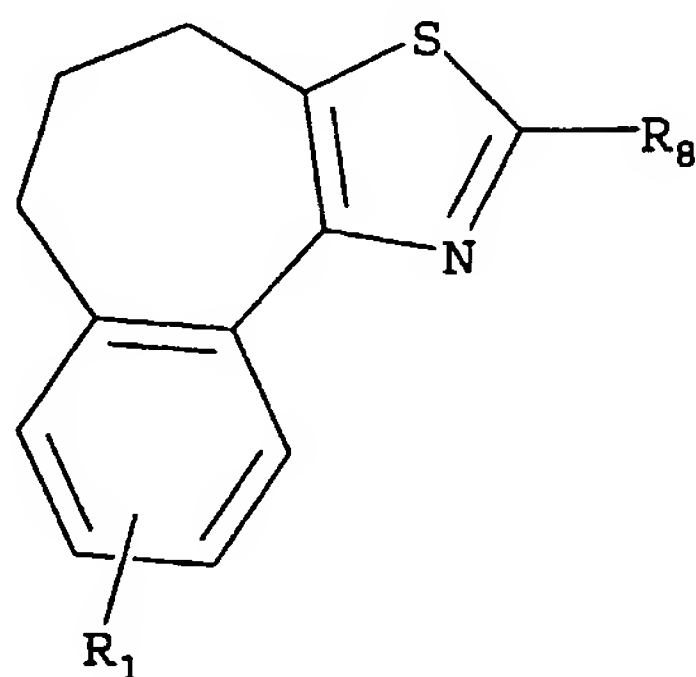
In one embodiment, ³⁶ the compound has the structure:



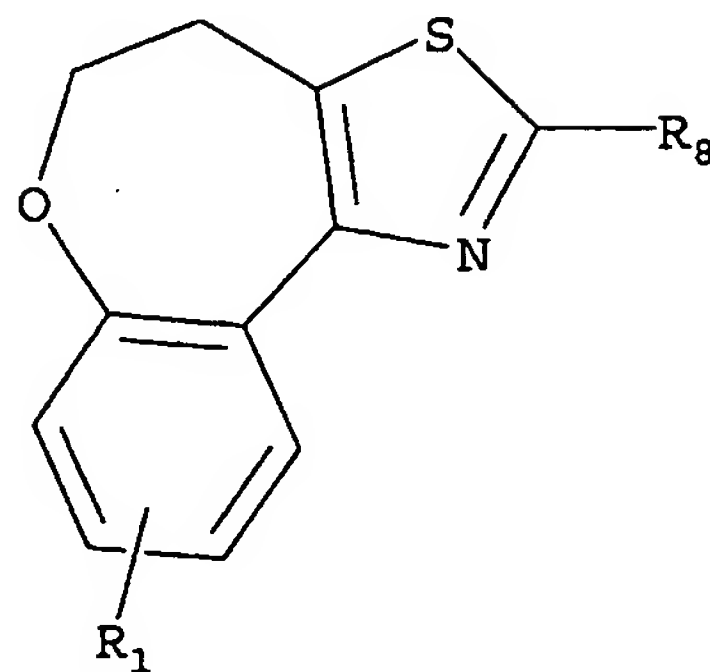
wherein X is CR_5R_6 , O or NR_5 .

5

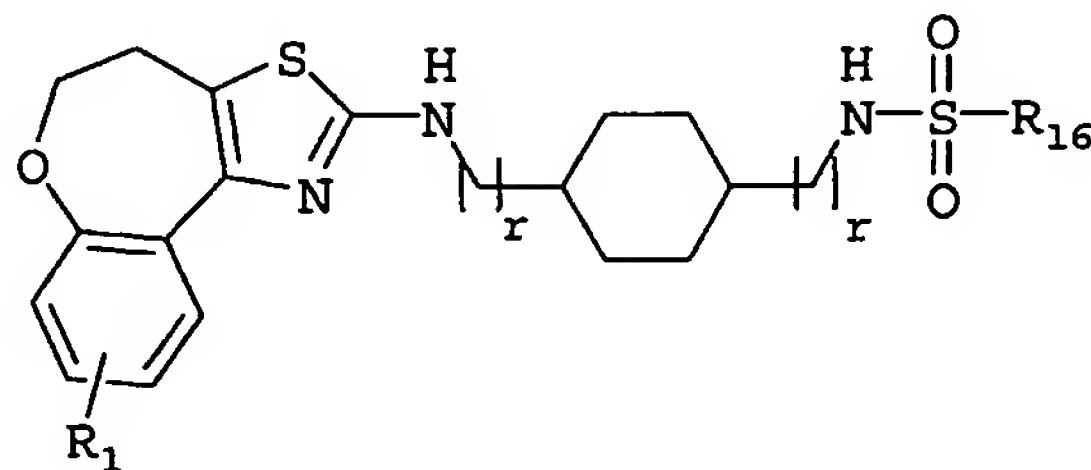
In another embodiment, the compound has the structure:



37
In still another embodiment, the compound has the structure:

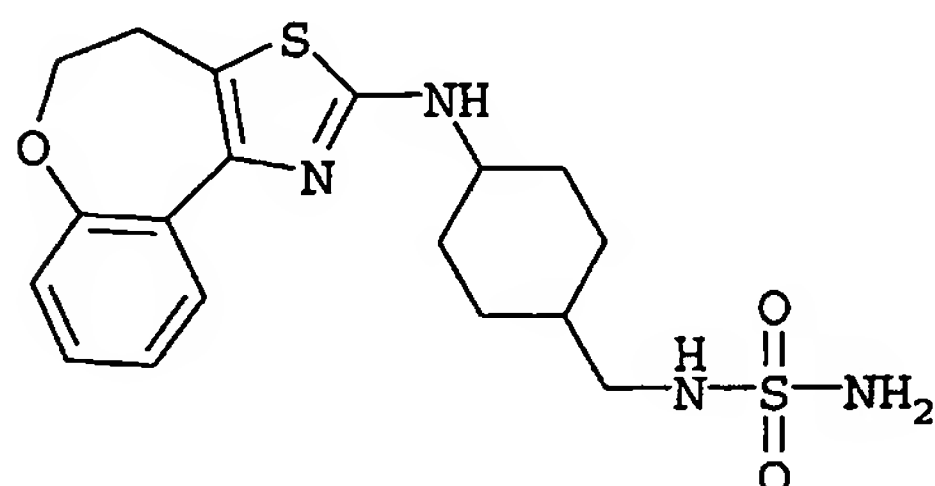
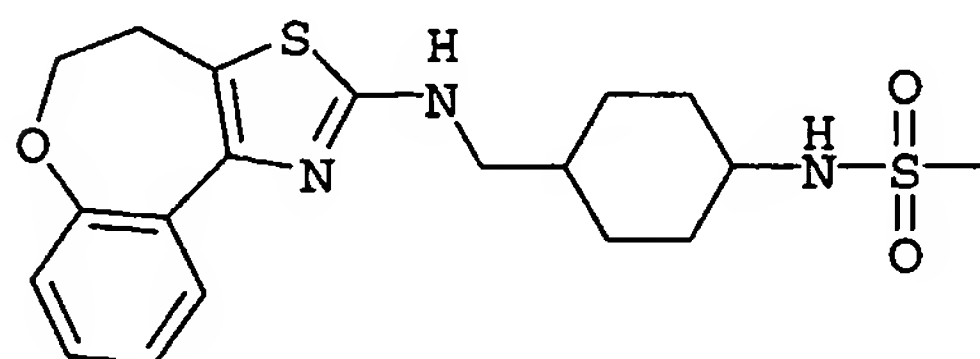
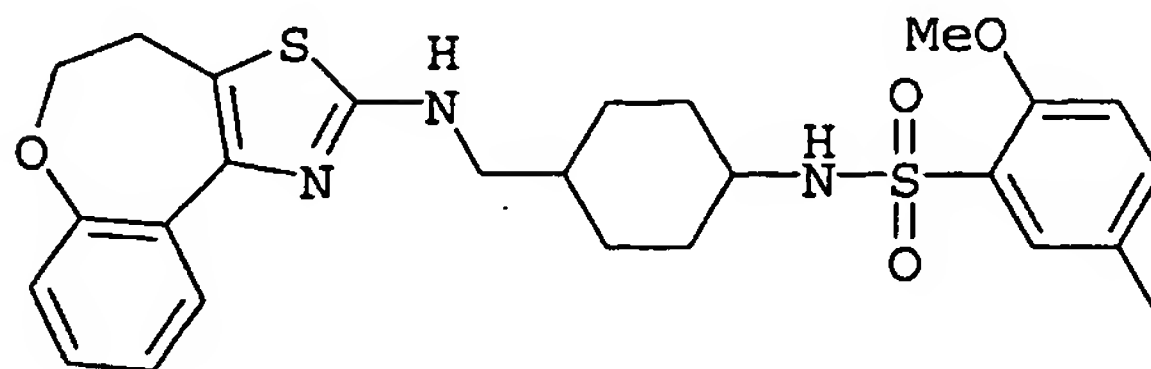


5 In a further embodiment, the compound has the structure:

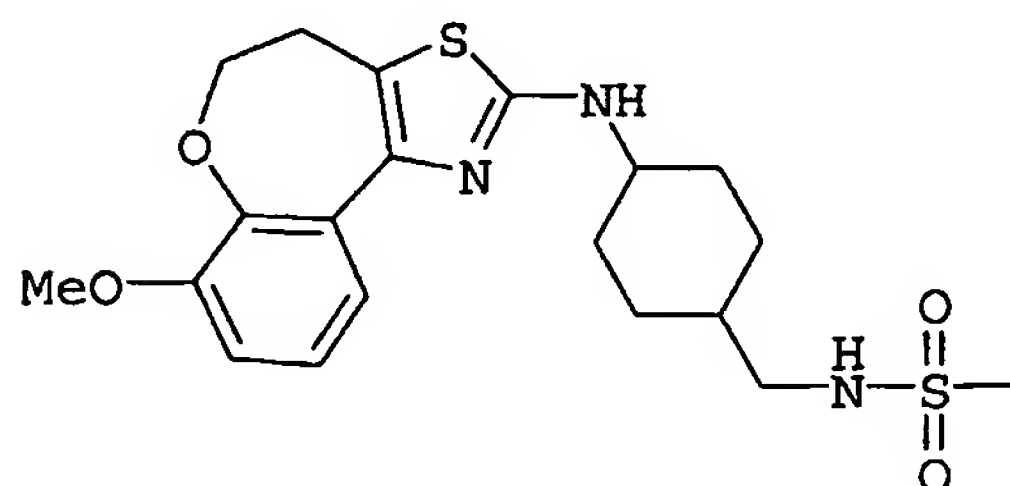


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In still further embodiments, the compound has the structure selected from the group consisting of:

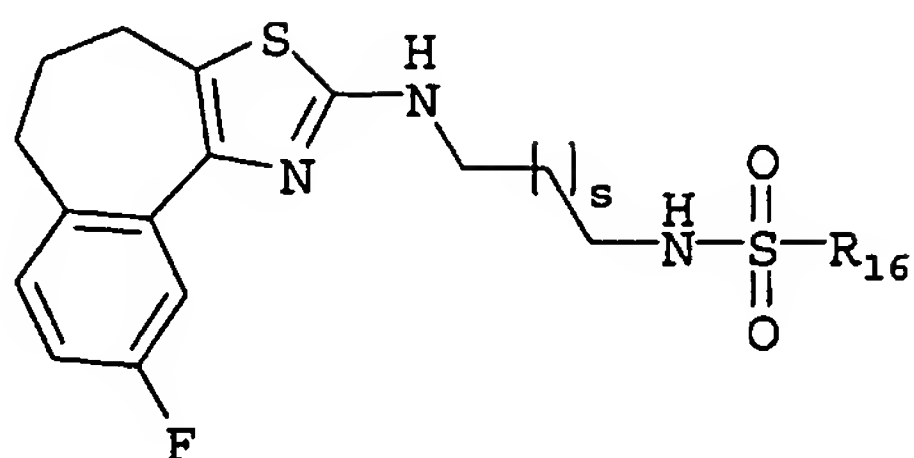


, and



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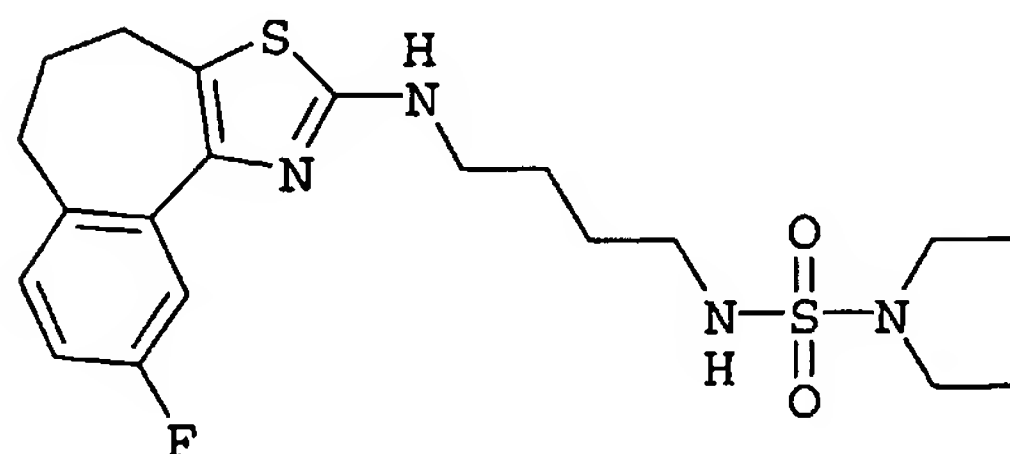
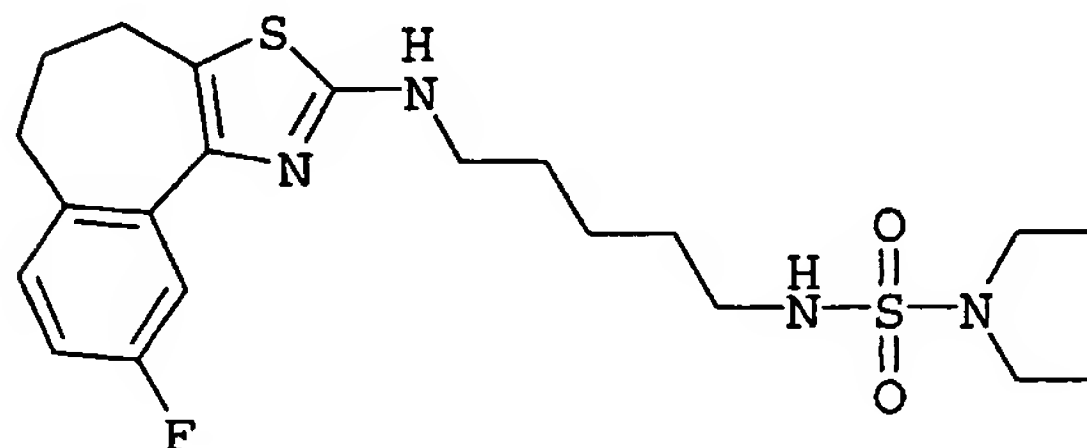
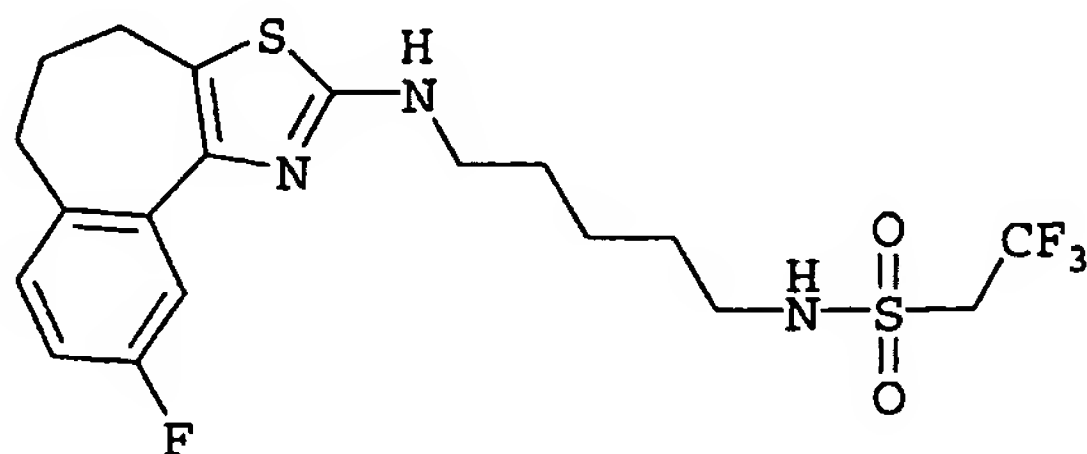
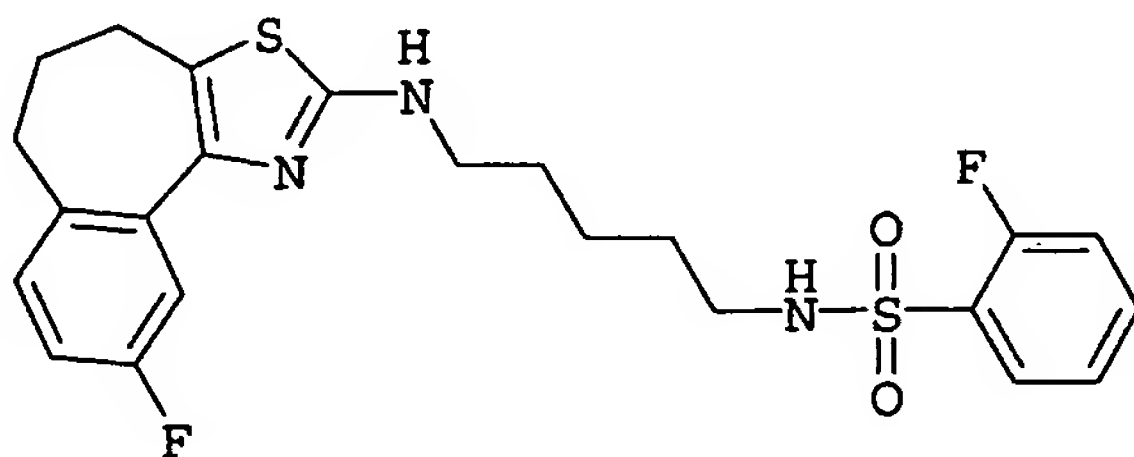
In another embodiment, the compound has the structure:

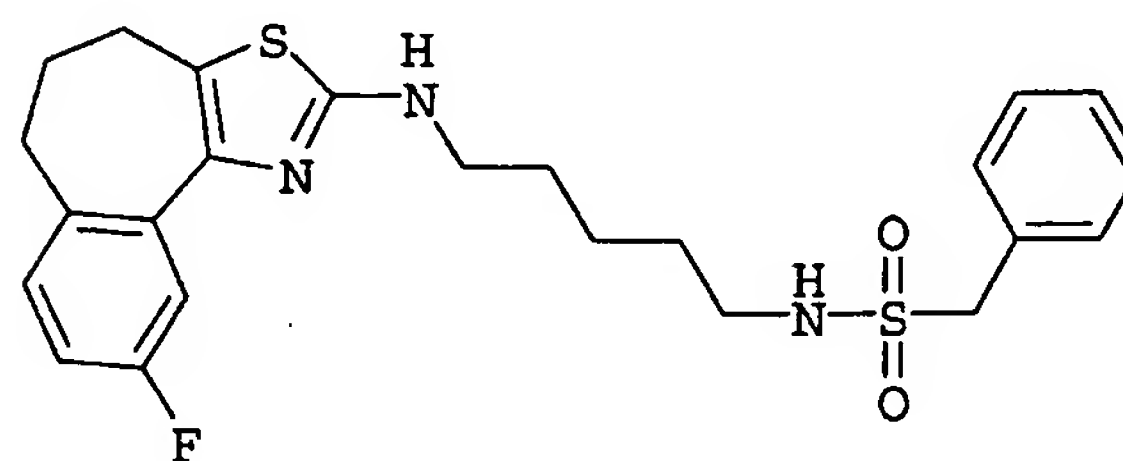
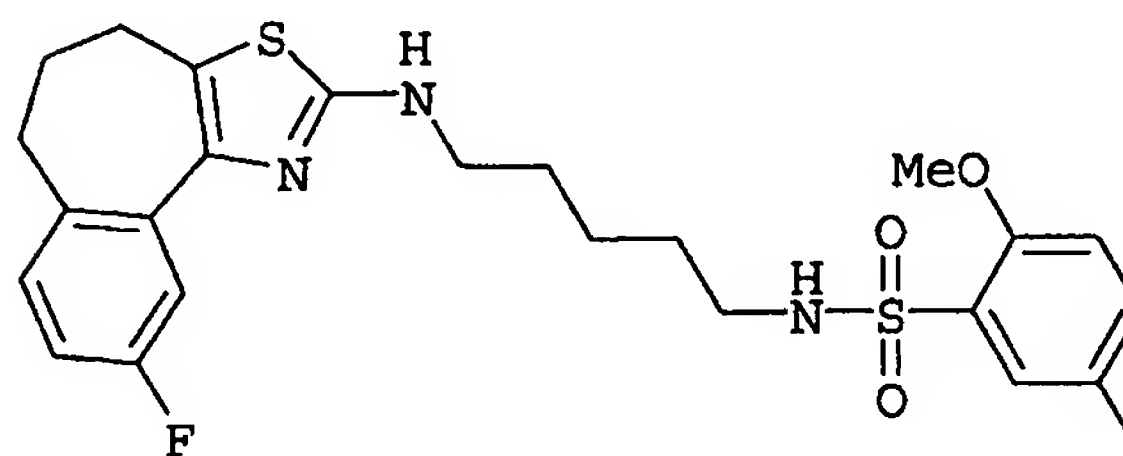
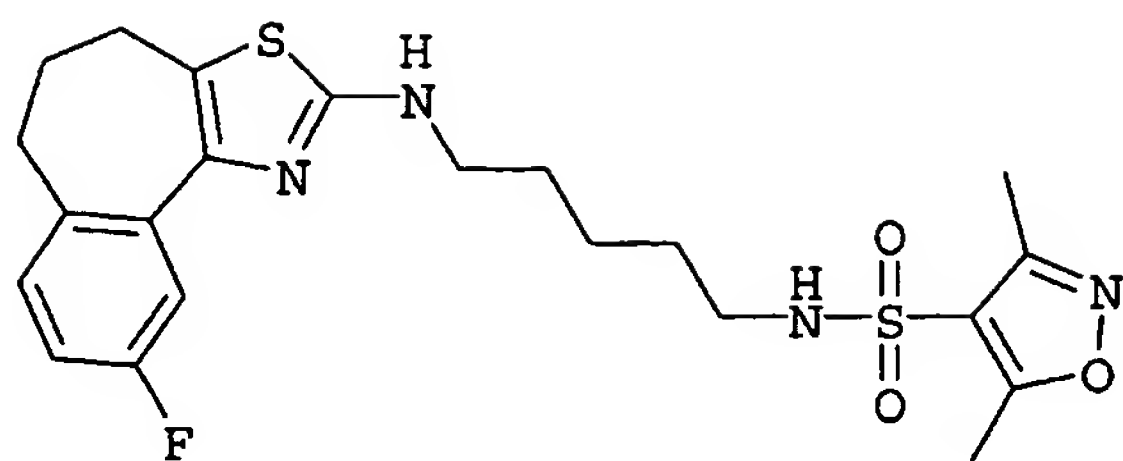


wherein *s* is 2, 3 or 4.

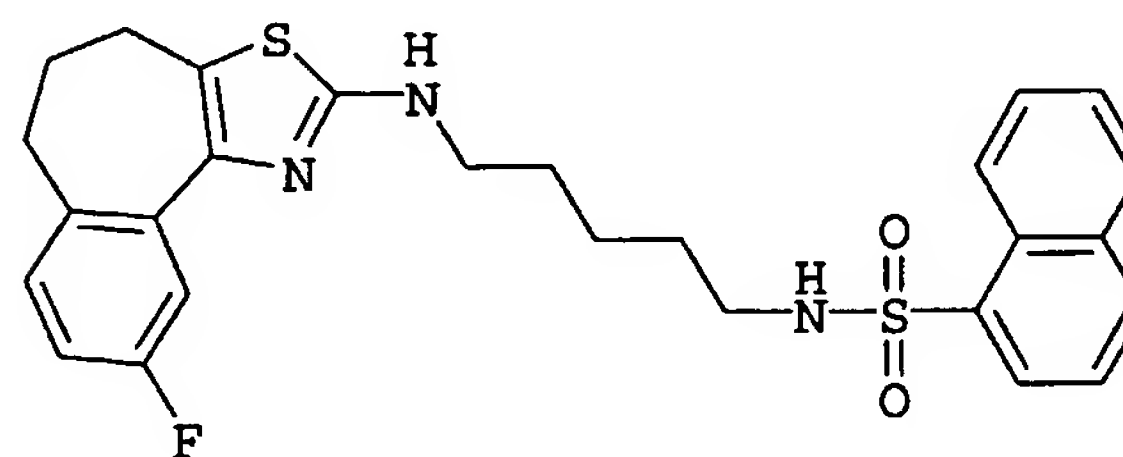
5

In still other embodiments, the compound has the structure selected from the group consisting of:



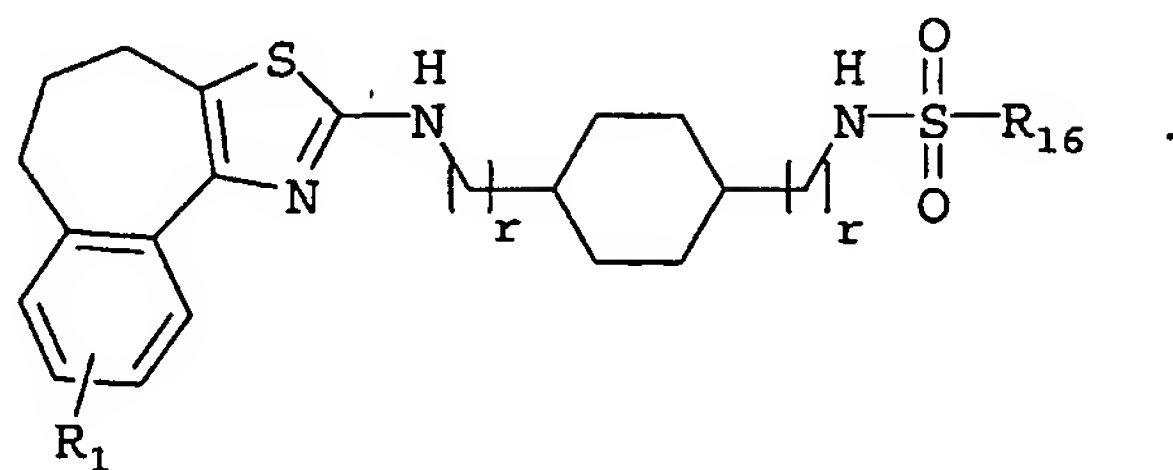


, and

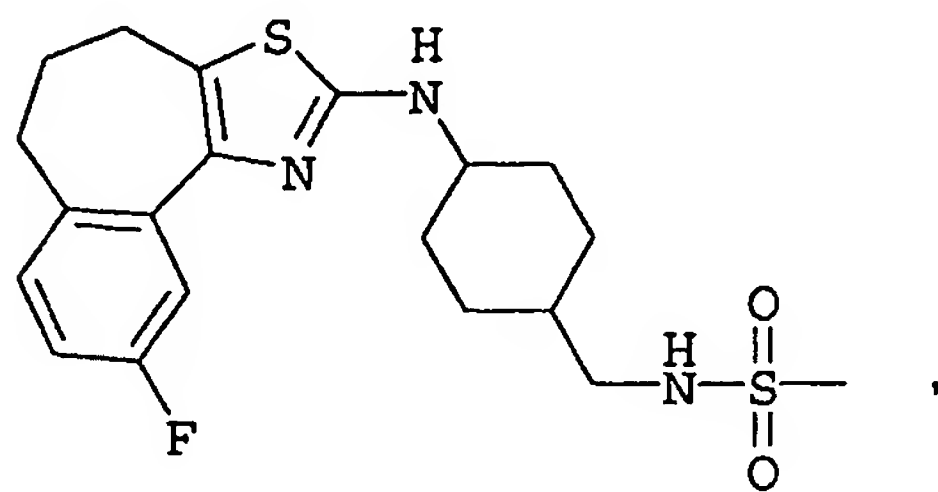
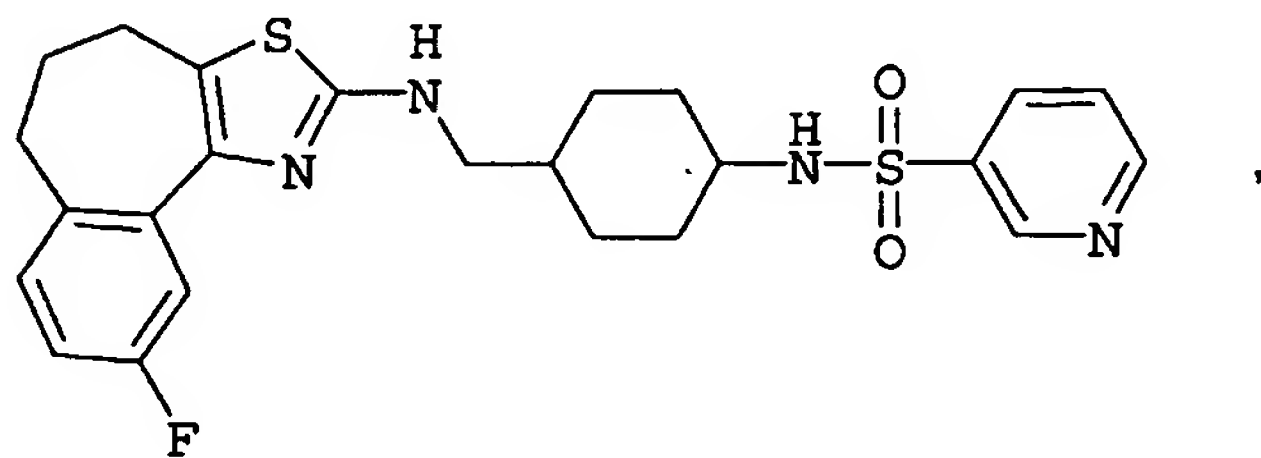
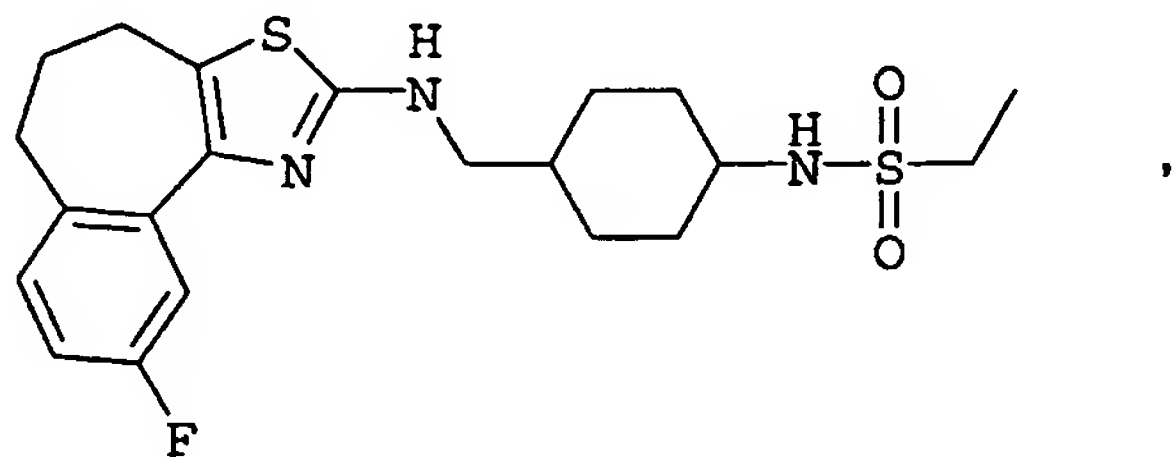


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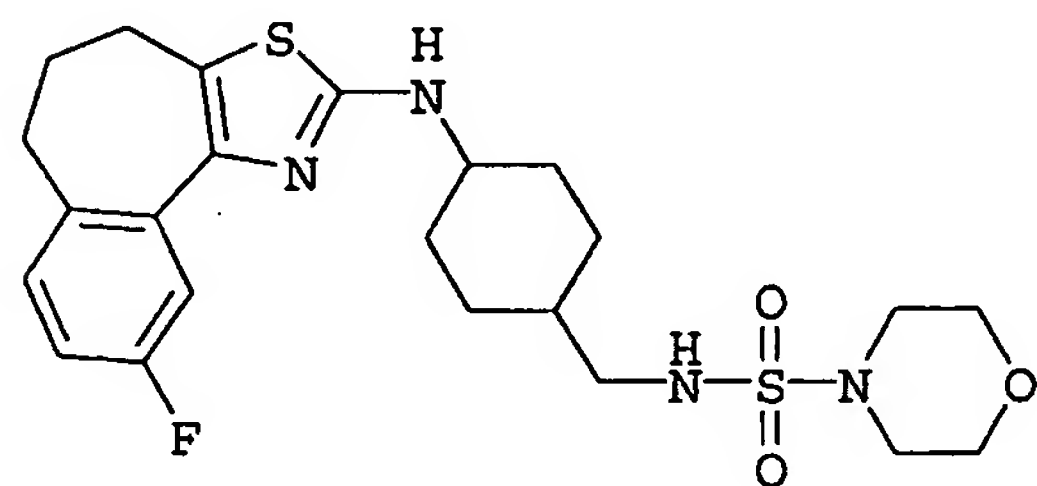
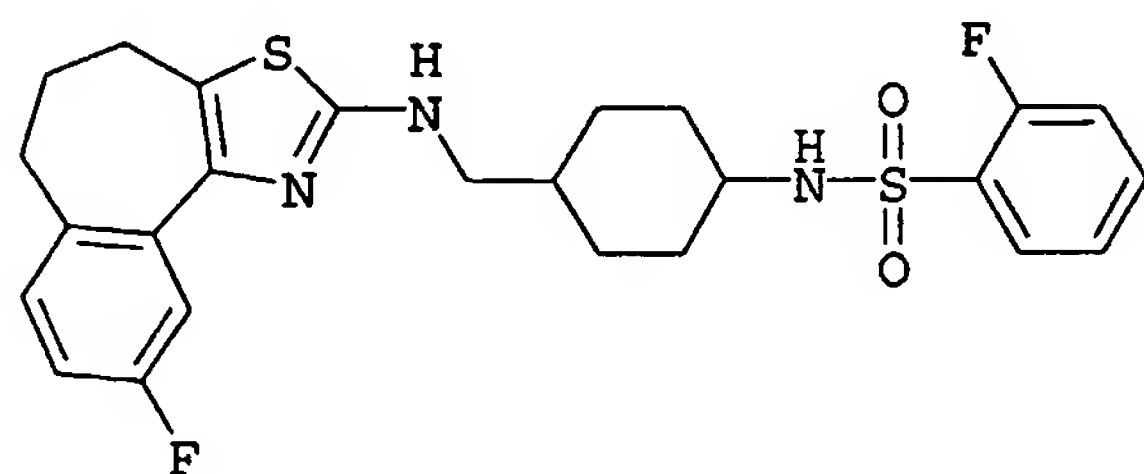
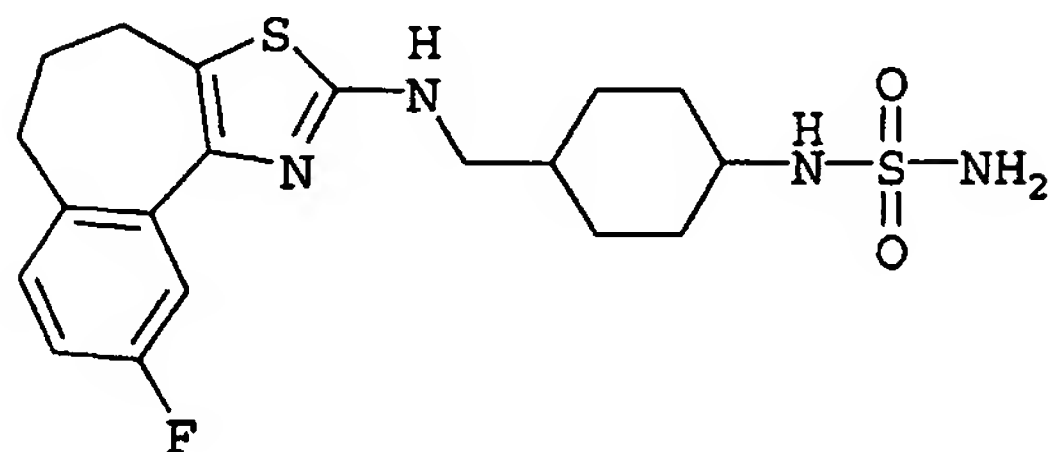
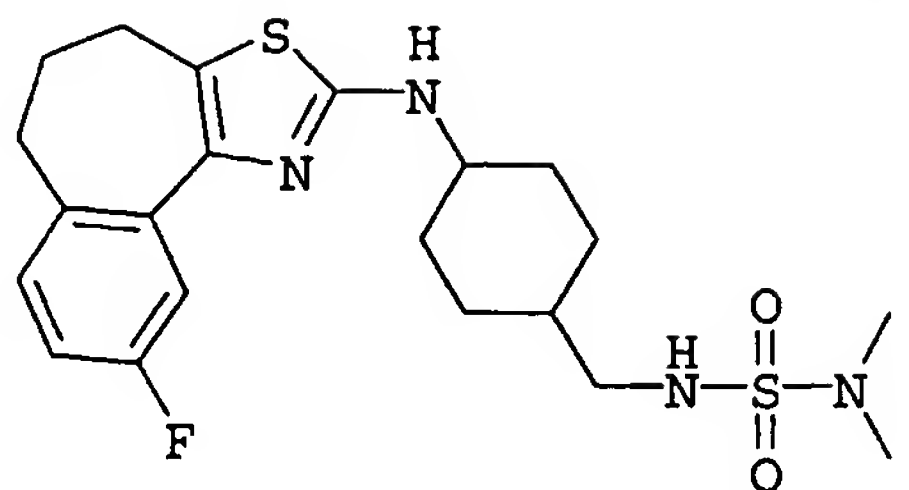
In a further embodiment, the compound has the structure:

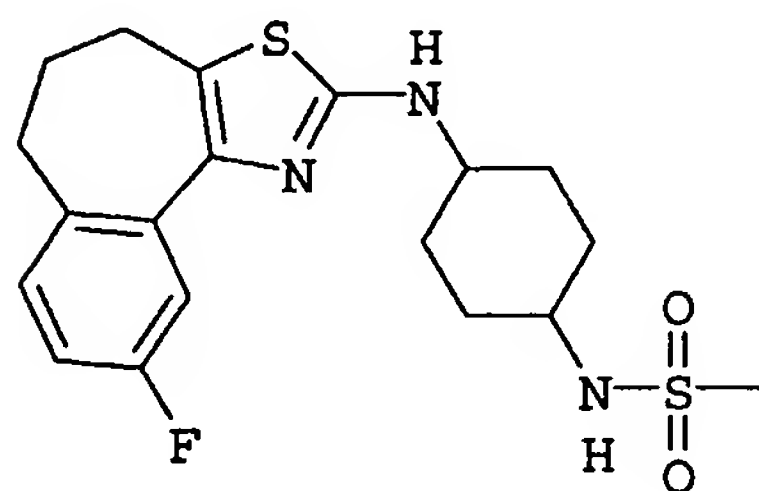
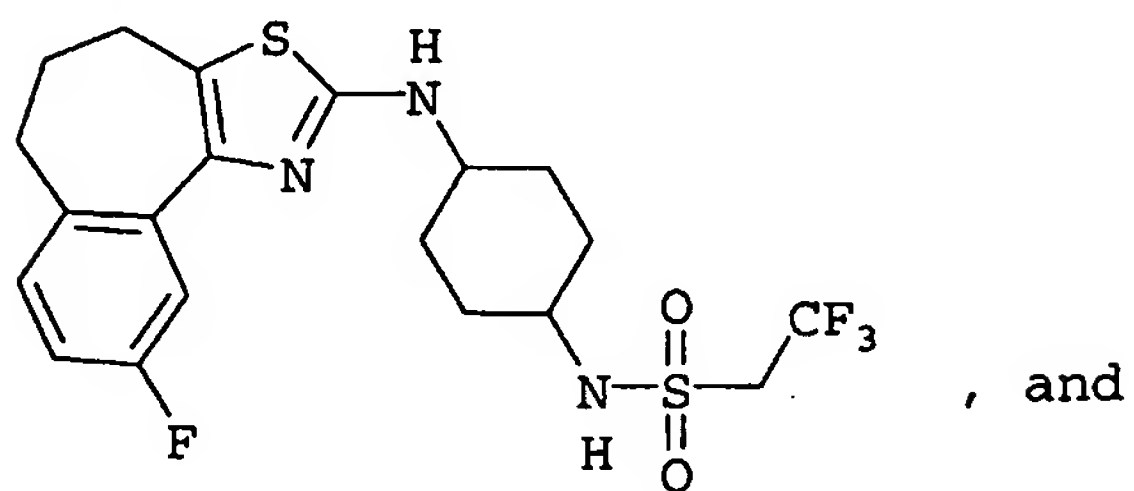
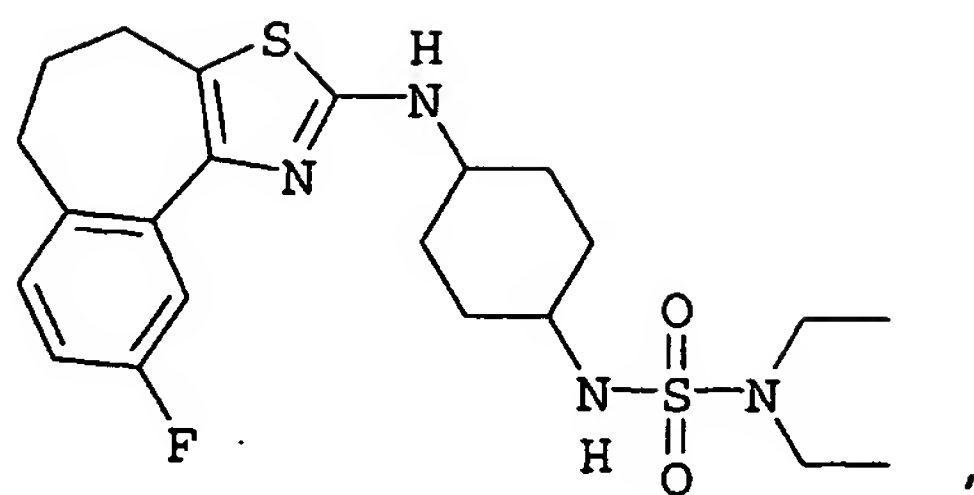


In still further embodiments, the compound has the structure selected from the group consisting of:



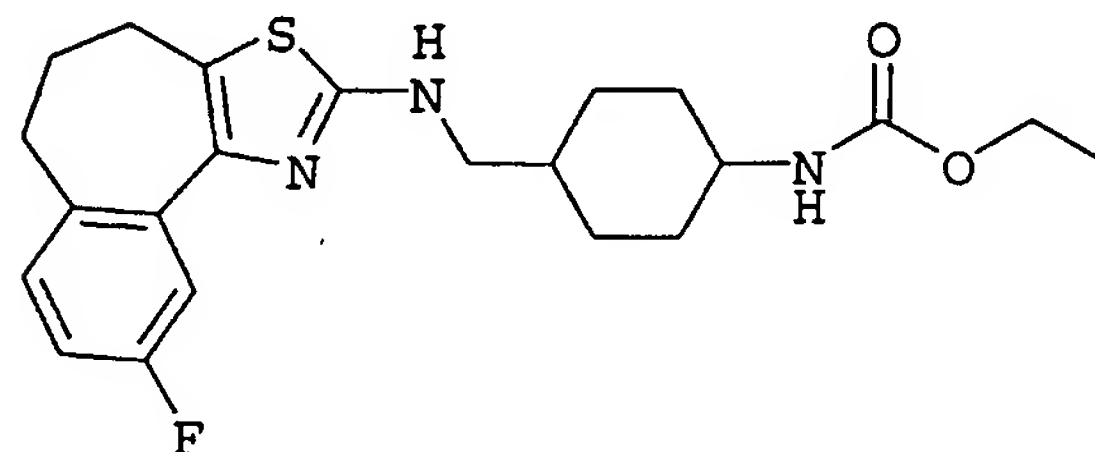
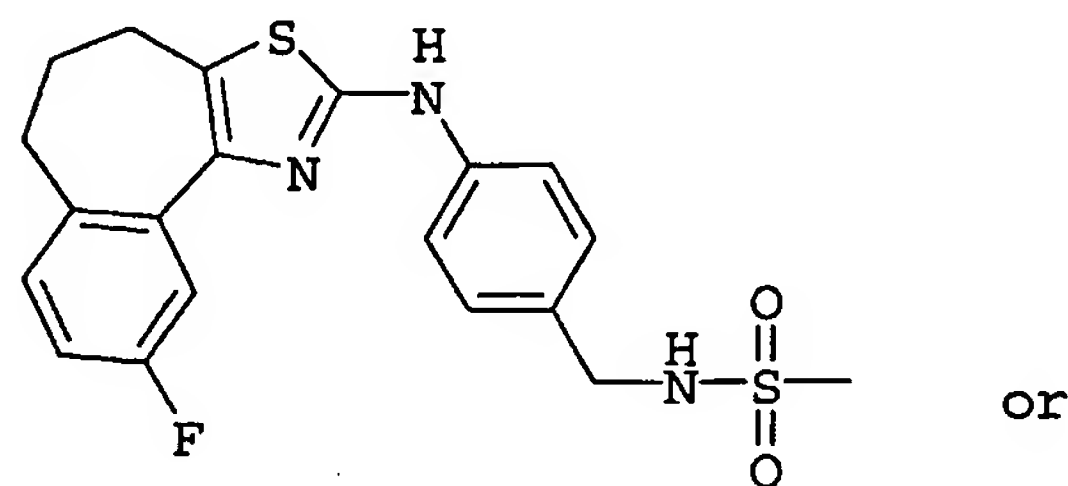
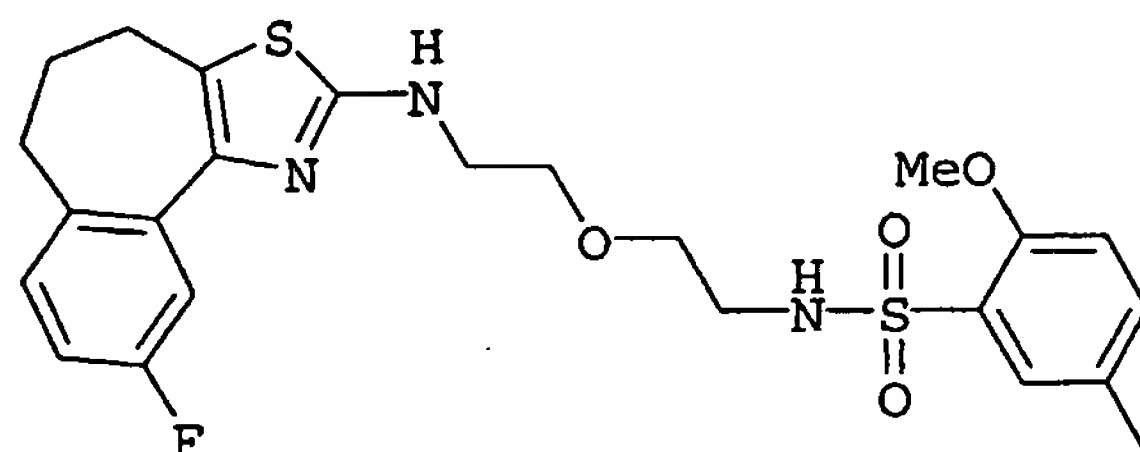
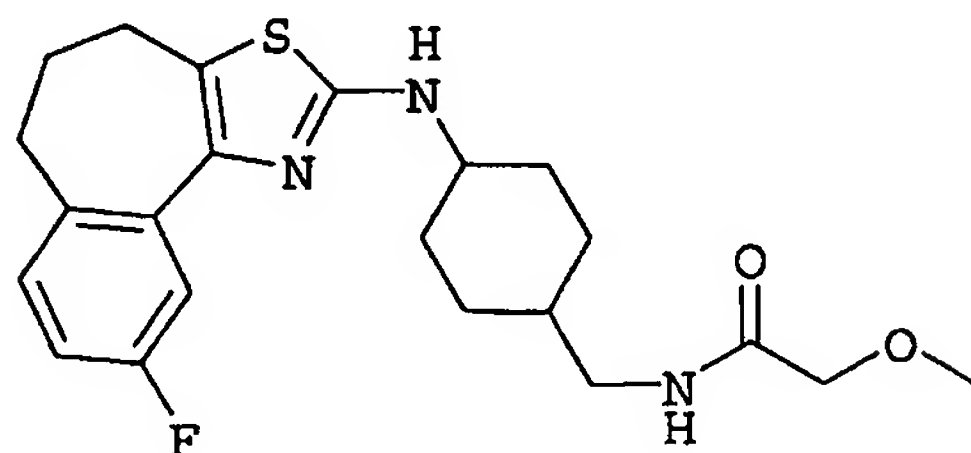
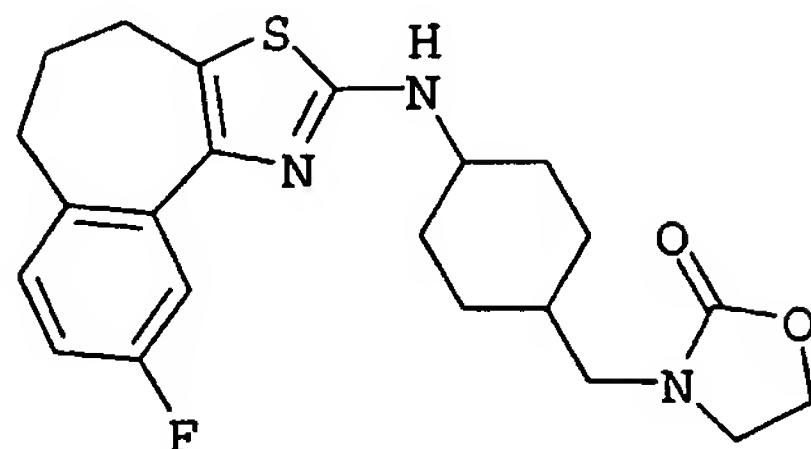
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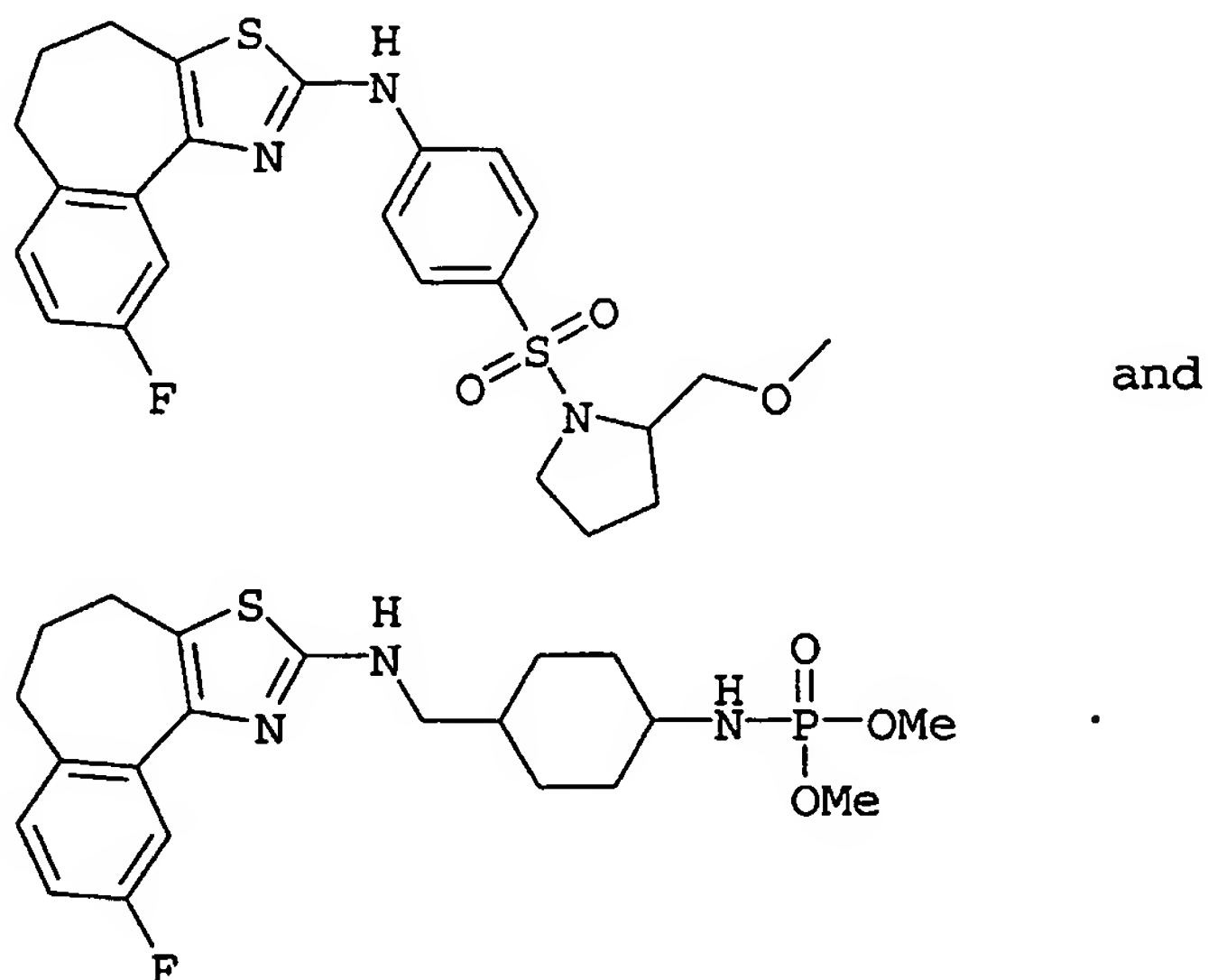
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In still other embodiments, the compound has the structure:



45

In still further embodiments, the compound has the structure selected from the group consisting of:



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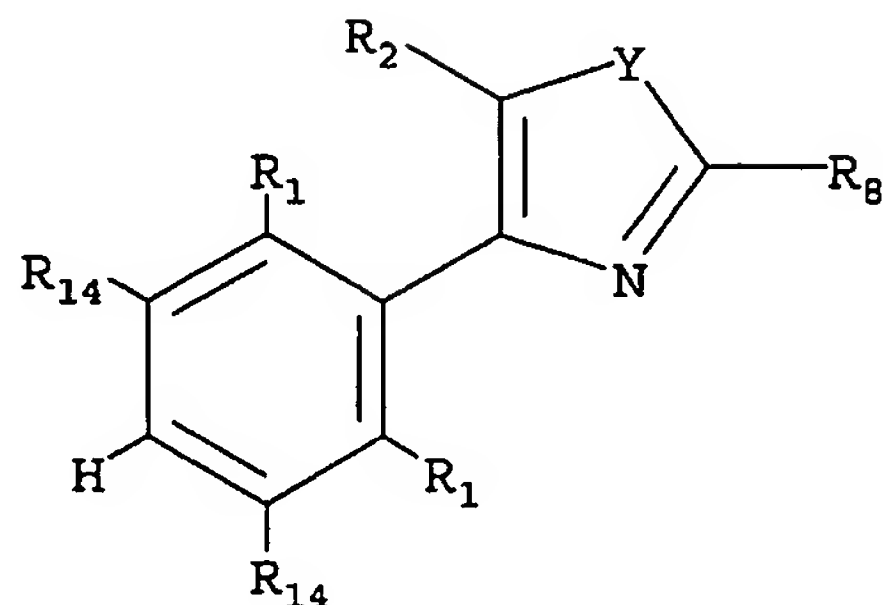
In the present invention as relates to tricyclic compounds, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more heteroatoms such as oxygen, sulfur, and nitrogen. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinolizinyl, and 2,1,3-

20

benzothiazolyl. Furthermore, any of the heteroaryl groups recited above may be substituted with thienyl, isoxazolyl, or pyridyl.

B. Bicyclic Compounds

This invention provides a compound having the structure:



5 wherein Y is O, S or NH;

wherein each R_{14} independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl; provided that if one R_{14} is phenyl, heteroaryl or C₁-C₇ phenylalkyl, the other R_{14} is H;

wherein each R_1 independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

wherein R_2 is H, straight chained or branched C_1 - C_4 alkyl,
 $-(CH_2)_tOR_5$, phenyl optionally substituted with one or more
 of of F, Cl, Br, $-CF_3$, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, -
 5 $(CH_2)_nOR_5$, or straight chained or branched C_1 - C_4 alkyl;

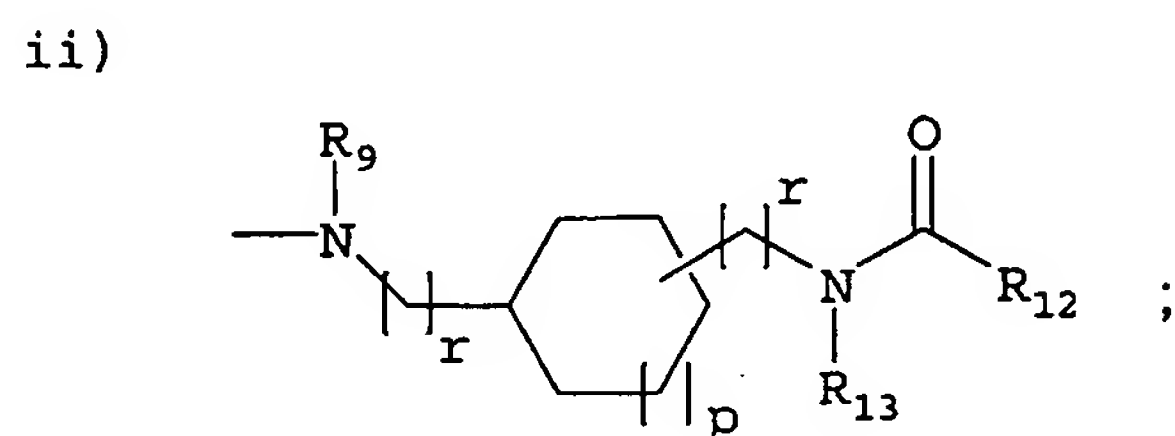
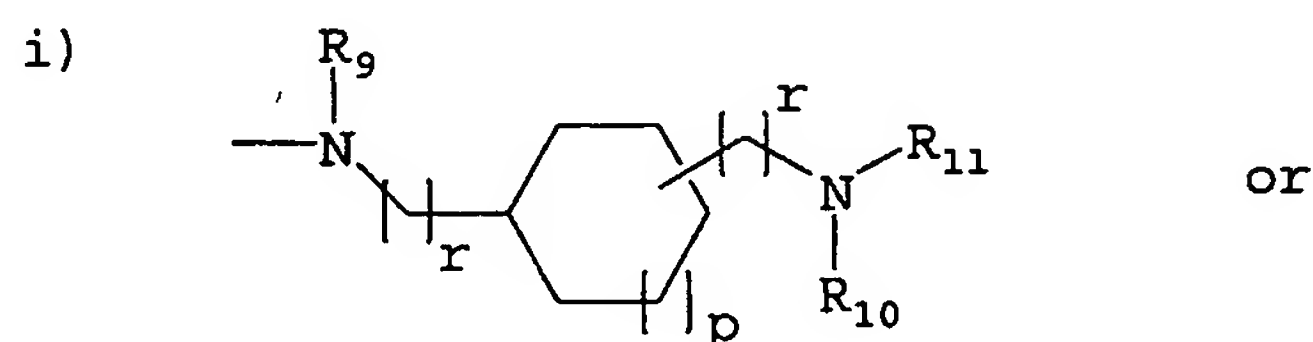
wherein R_5 is independently H; or straight chained or
 branched C_1 - C_7 alkyl;

10 wherein R_6 is independently H; or straight chained or
 branched C_1 - C_7 alkyl;

wherein each n independently is an integer from 0 to 6
 inclusive;

15

wherein R_8 is



20

provided that R_1 or R_{14} cannot be $-OH$, when R_8 is (ii);

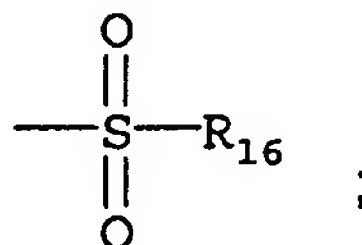
wherein R_9 is independently H; or straight chained or
 branched C_1 - C_4 alkyl;

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wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



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wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl; or $(CH_2)_nOR_{17}$;

10

wherein R_{13} is independently $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, or straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

15

20

25

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

30

50

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more
 5 of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or
 10 cycloalkenyl; or phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$,
 15 ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl;
 20 wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, or straight
 25 chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or
 30 branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; or phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6

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heteroarylalkyl may be substituted with one or more
 of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -
 (CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -
 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl,
 5 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; -(CH₂)_uOR₅; -
 10 (CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 or phenyl or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆
 15 phenylalkyl may be substituted with one or more of F, Cl,
 Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -
 (CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -
 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 20 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which
 they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-
 25 piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-
 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted
 with one or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -
 (CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -
 (CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl,
 30 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 cycloalkyl or cycloalkenyl, or phenyl or heteroaryl;
 wherein if -(CH₂)_nNR₅R₆, -(CH₂)_nOR₅, or -(CH₂)_nNR₅COR₅ are
 in the 2-position, then n is not 0; wherein the phenyl or

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heteroaryl may be substituted with one or more
of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -
(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -
(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-
5 C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl,
straight chained or branched C₂-C₇ alkenyl or alkynyl, or
C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which
10 they are attached are morpholinyl, thiomorpholinyl,
[1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or
[1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl,
[1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or
[1,4]diazepanyl is optionally substituted with straight
15 chained or branched C₁-C₅ alkyl or (CH₂)_tOR₅; and wherein
the nitrogen atom of the piperazinyl or [1,4]diazepanyl
ring may be optionally substituted with -(CH₂)_uOR₅; -COR₅;
straight chained or branched C₁-C₅ alkyl; or phenyl;
wherein the phenyl may be substituted with one or more of
20 F, Cl, Br, -CN, -NO₂, -NR₅R₆, -(CH₂)_nOR₅, straight chained or
branched C₁-C₃ alkyl, perfluoroalkyl, polyfluoroalkyl, or
aminoalkyl;

wherein R₁₇ is straight chained or branched C₁-C₄ alkyl,
25 perfluoroalkyl, or polyfluoroalkyl;

wherein each p independently is an integer from 0 to 2
inclusive;

30 wherein each r independently is an integer from 0 to 3
inclusive;

wherein t is an integer from 1 to 4 inclusive;

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wherein each u independently is an integer from 2 to 4 inclusive;

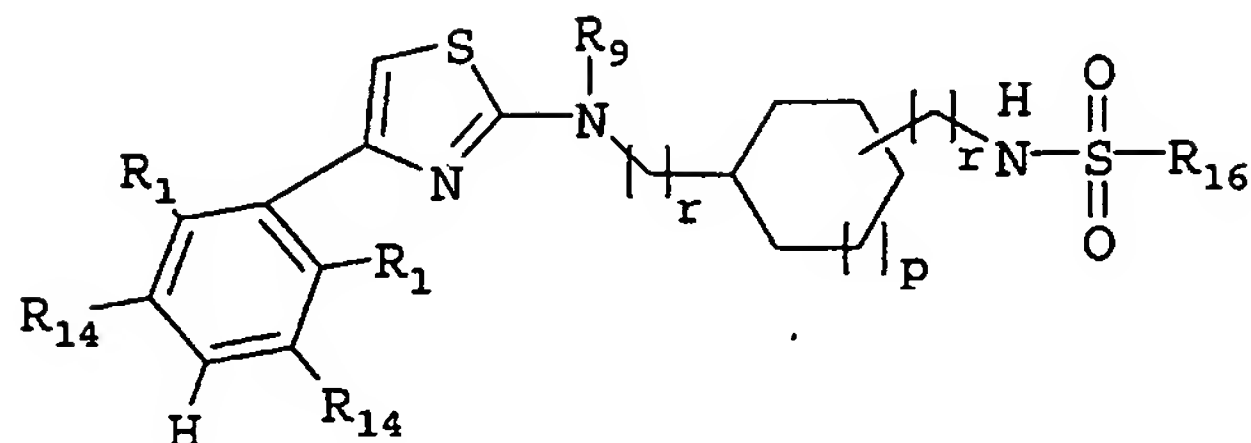
or a pharmaceutically acceptable salt thereof.

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In one embodiment, the compound comprises the (+) enantiomer. In another embodiment, the compound comprises the (-) enantiomer.

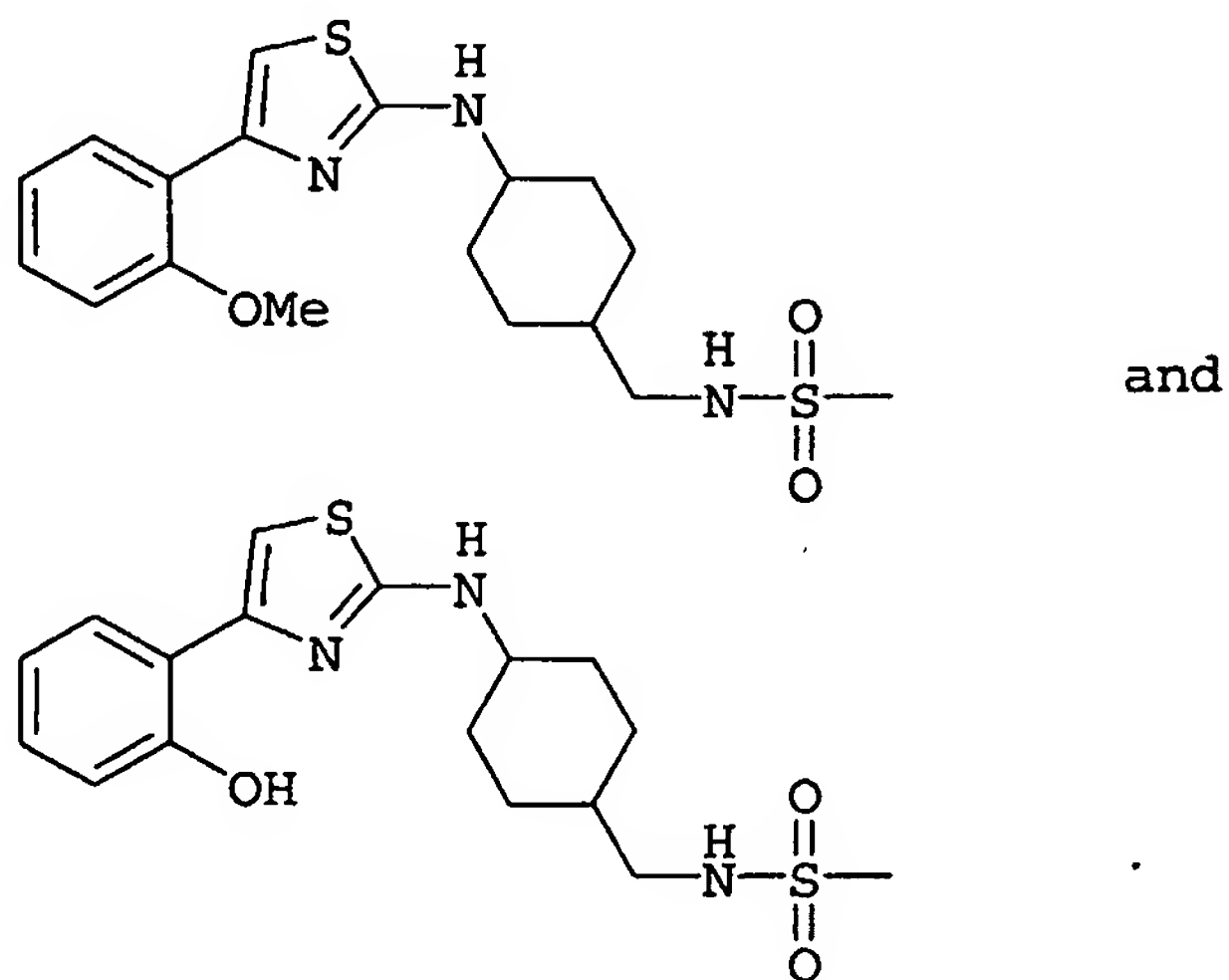
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In one embodiment, the compound has the structure:



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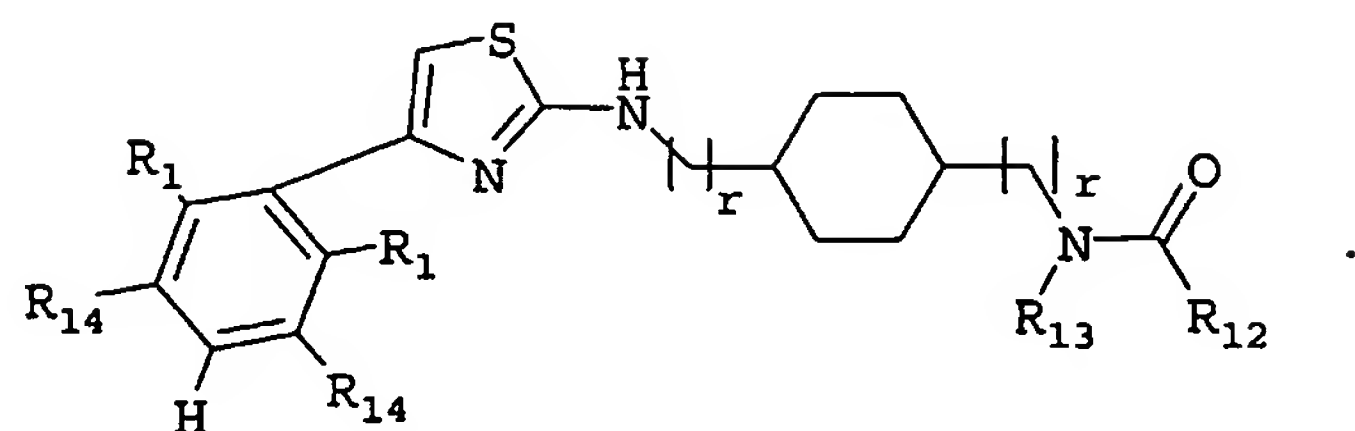
In further embodiments, the compound has the structure selected from the group consisting of:



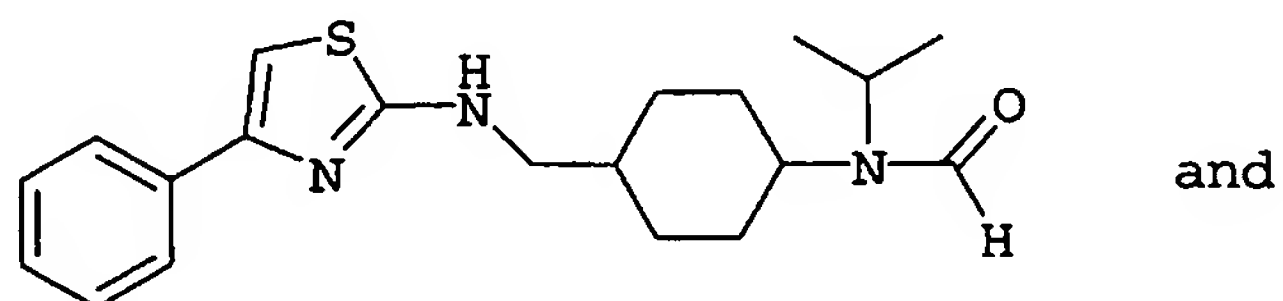
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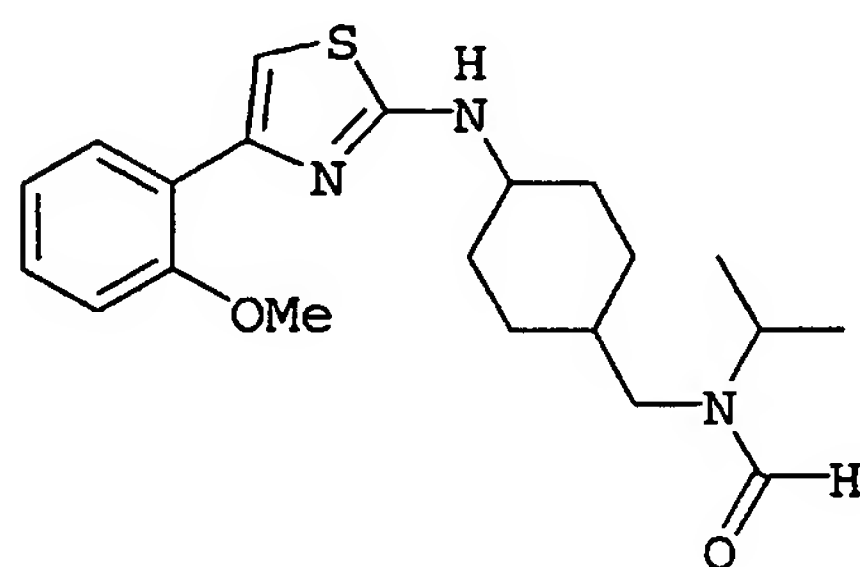
In another embodiment, the compound has the structure:



5 In further embodiment, the compound has the structure selected from the group consisting of:



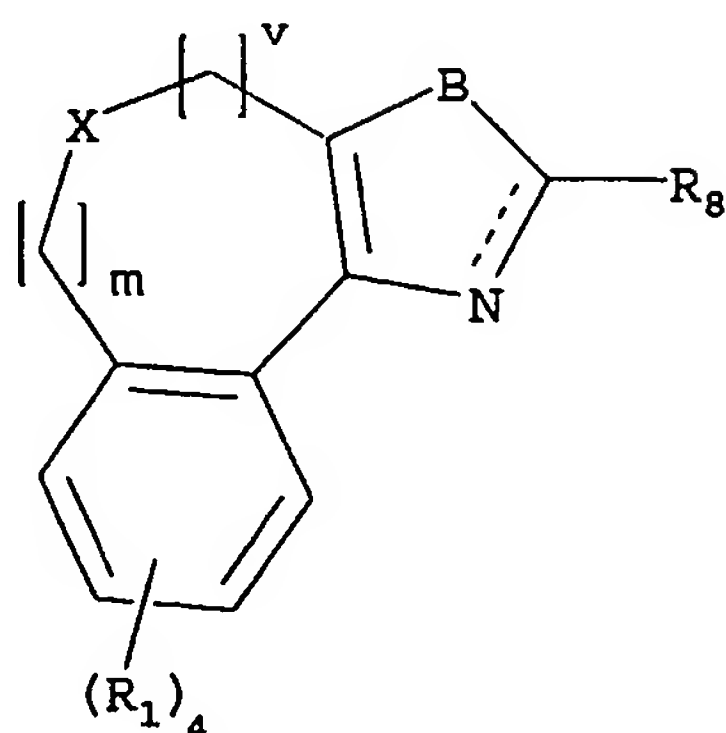
and



In the present invention as relates to bicyclic compounds, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one sulfur or nitrogen atom or one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyll, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinolizinyll, and 2,1,3-benzothiazolyl.

C. Tricyclic Compounds

The invention provides a compound having the structure:



5 wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

10 wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

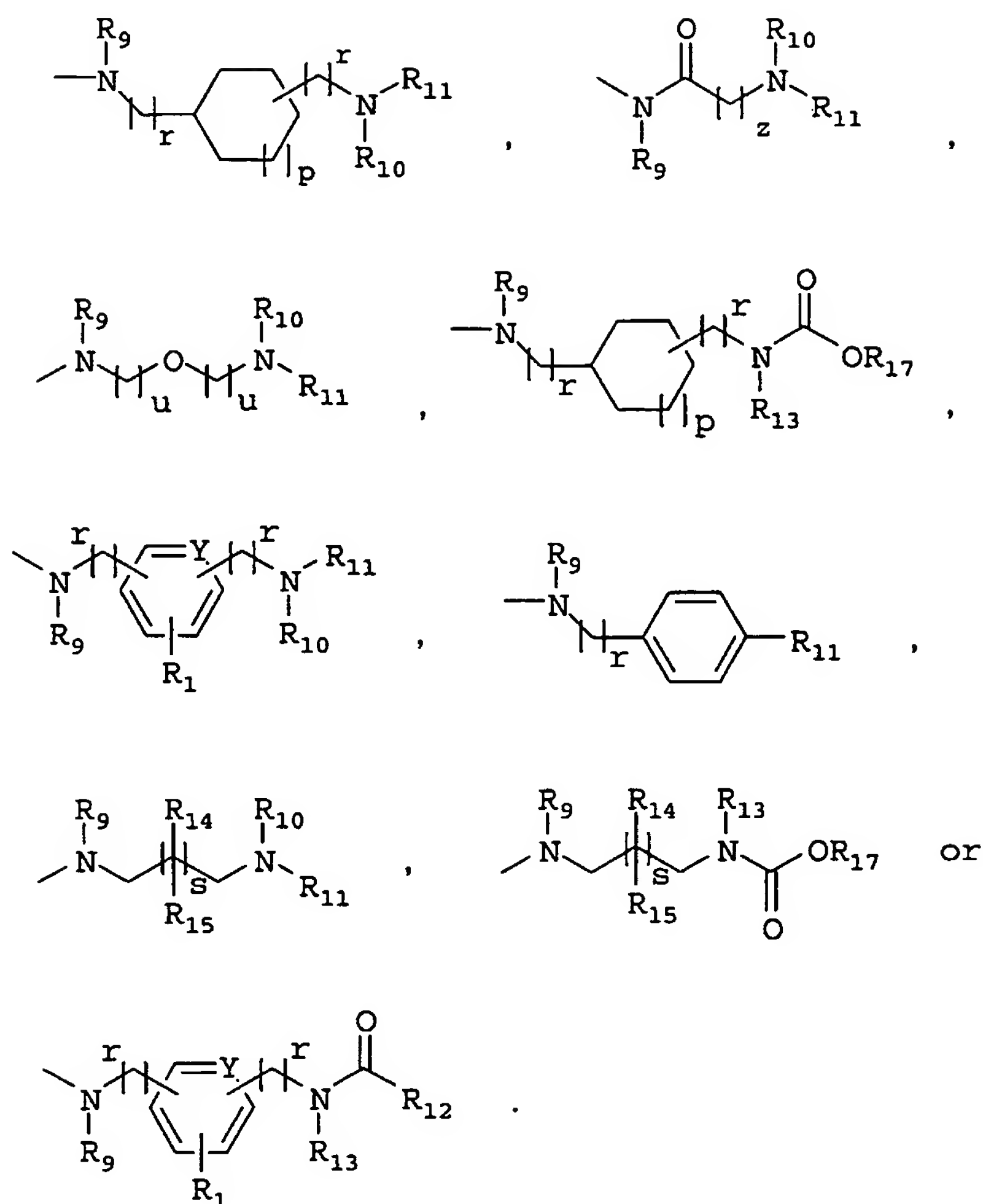
15

wherein B is O, NH or S;

wherein X is S, SO or SO₂;

20 wherein each n independently is an integer from 0 to 6 inclusive;

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wherein R_8 is

5

wherein Y is C or N;

wherein R_7 is independently straight chained or branched
 10 C_1 - C_7 alkyl;

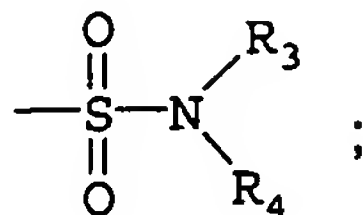
wherein R_9 is independently H; or straight chained or
 branched C_1 - C_4 alkyl;

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wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is

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wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$;

10

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

30

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wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

5

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, C_1 - C_6 phenylalkyl or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

20

wherein R_4 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

30

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or R_3 and R_4 taken together with the nitrogen atom to which they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, $-(CH_2)_nNR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

20

or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C_1 - C_5 alkyl or $(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; $-COR_5$; $-CO_2R_5$; straight chained or branched C_1 - C_5 alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nOR_5$, straight chained or branched C_1 - C_3 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

30

wherein R_{17} is straight chained or branched C_1 - C_4 alkyl, perfluoroalkyl, or polyfluoroalkyl;

5 wherein m is 0 or 1;

wherein each p independently is an integer from 0 to 2 inclusive;

10 wherein each r independently is an integer from 0 to 3 inclusive;

wherein each s independently is an integer from 1 to 6 inclusive;

15

wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to 4 inclusive;

20

wherein v is 1 or 2;

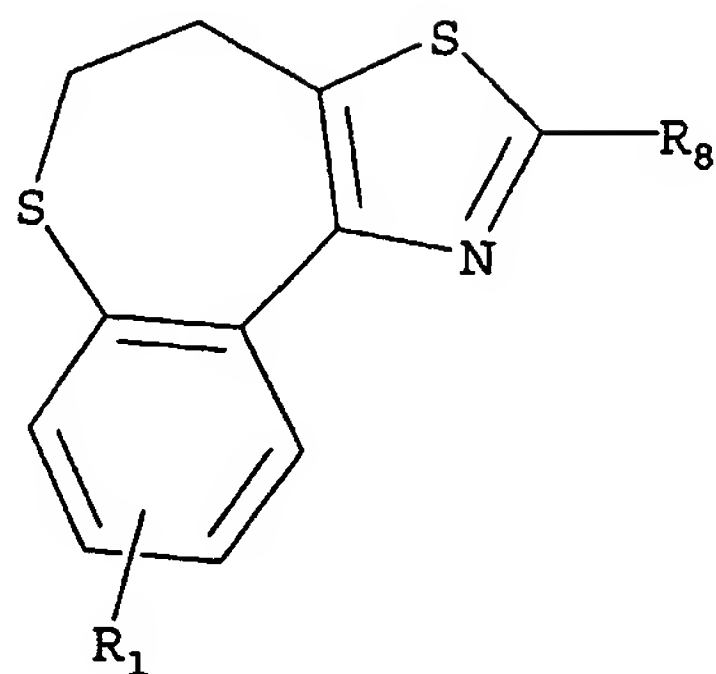
with the proviso that when v is 2, m is 0;

25 wherein z is an integer from 2 to 7;

or a pharmaceutically acceptable salt thereof.

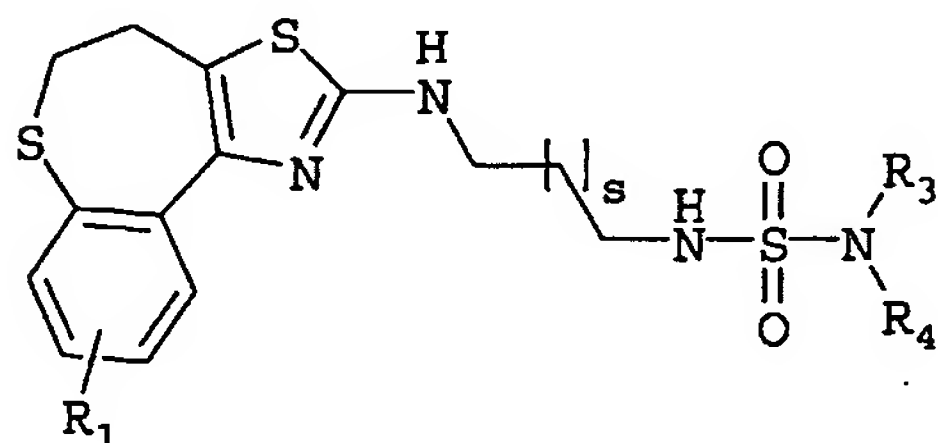
30 In one embodiment, the compound comprises the (+) enantiomer. In another embodiment, the compound comprises the (-) enantiomer.

In one embodiment, the ⁶³ compound has the structure:



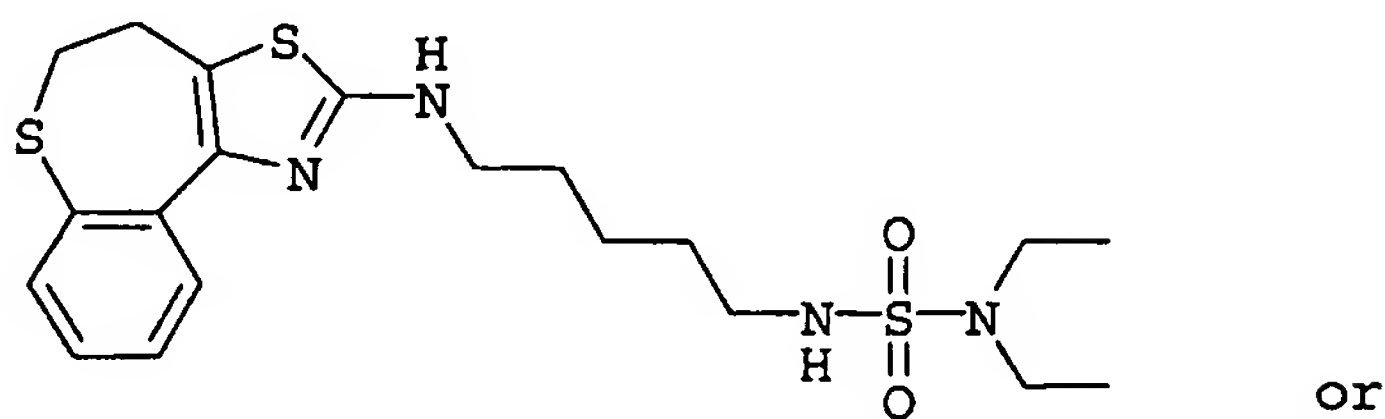
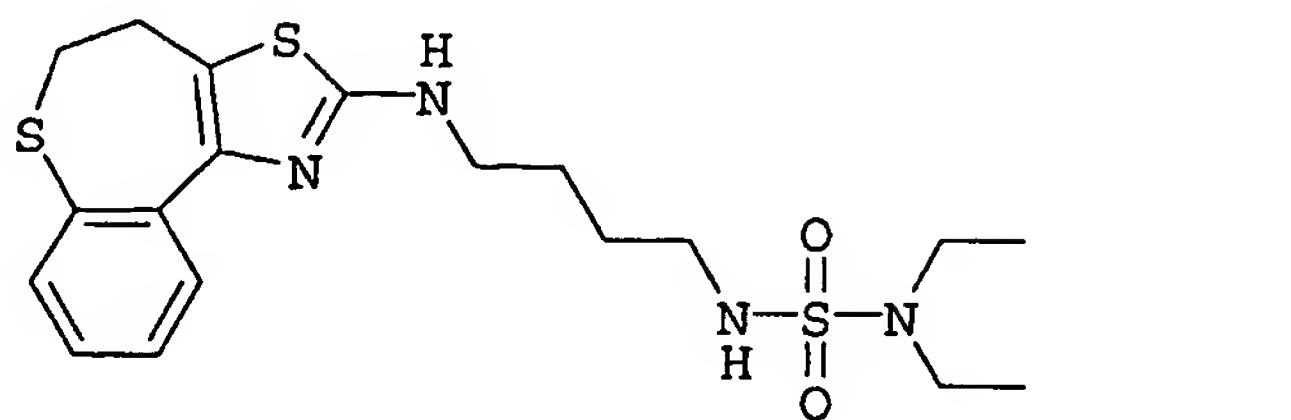
In another embodiment, the compound has the structure:

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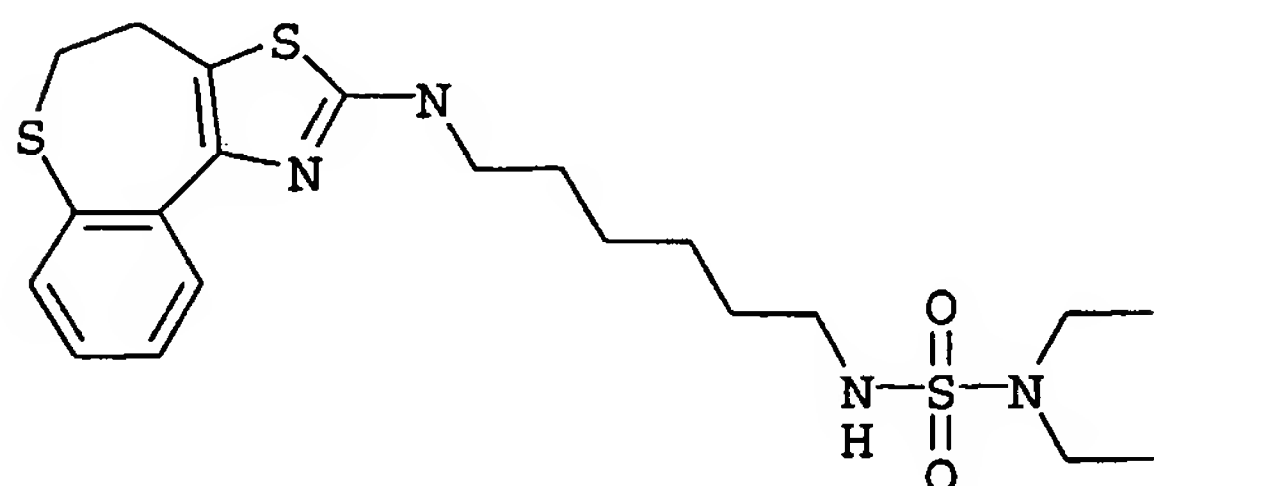


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In still other embodiments, the compound has the structure:

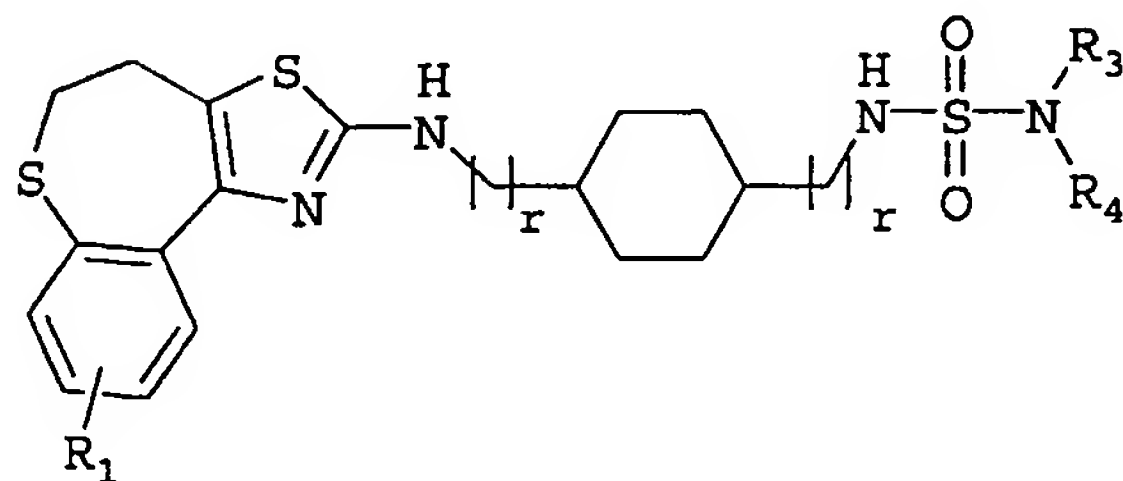


or



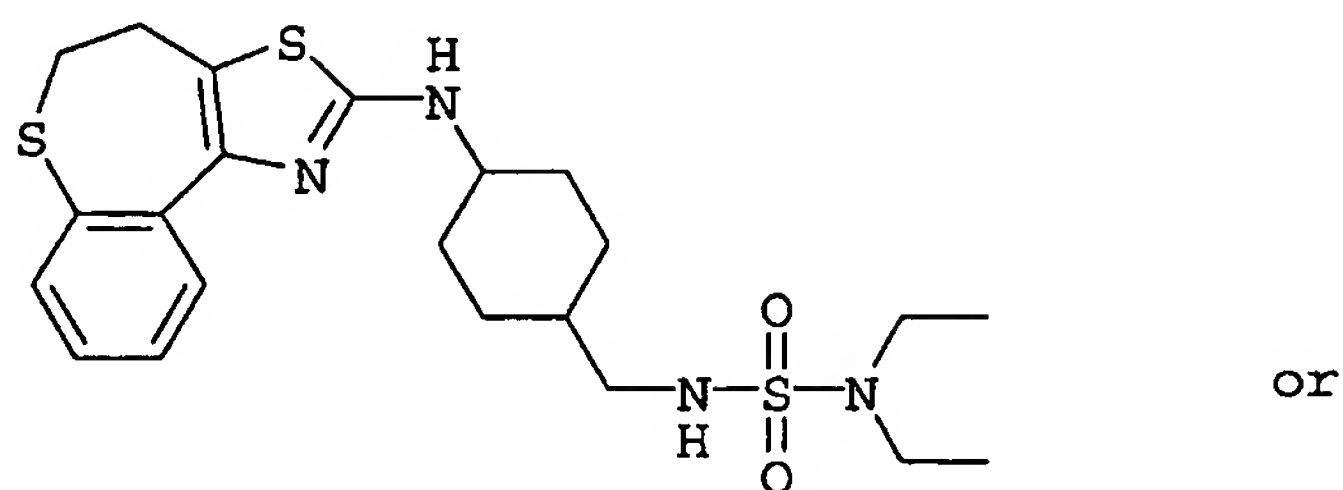
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In a further embodiment, the compound has the structure:

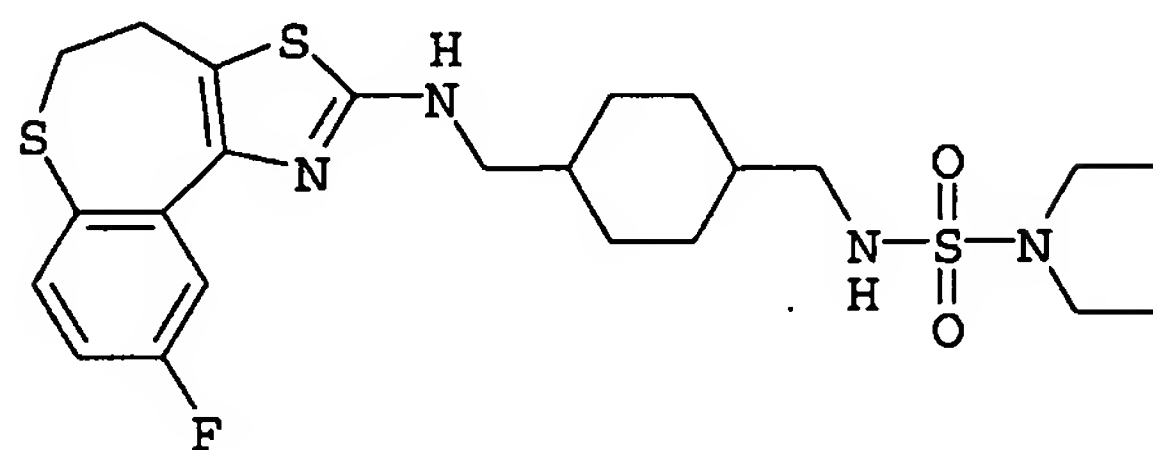


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In still further embodiments, the compound has the structure:

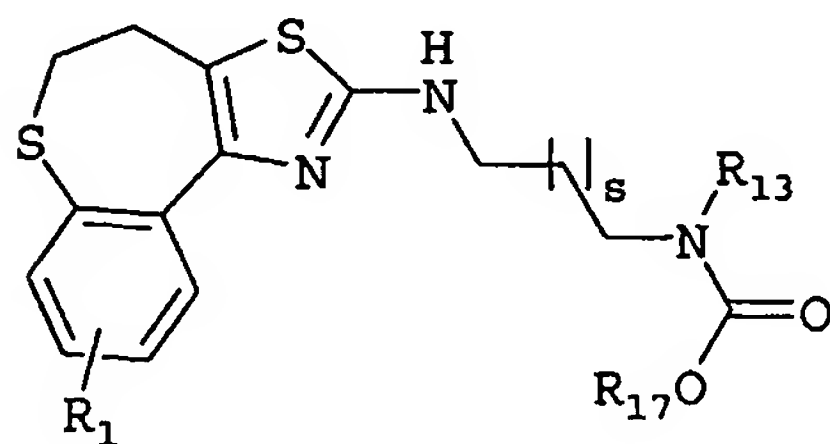


or



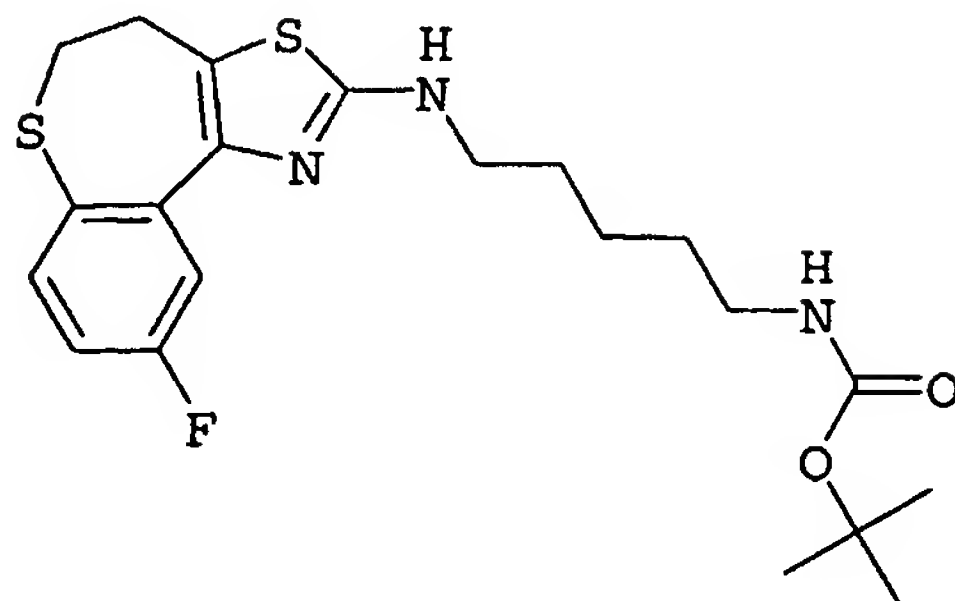
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In another embodiment, the compound has the structure:



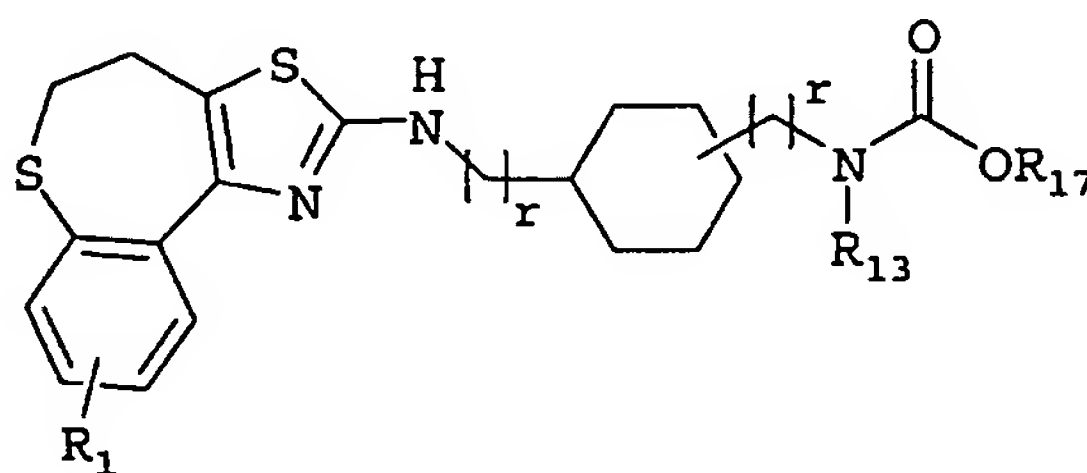
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In still another embodiment, the compound has the structure:



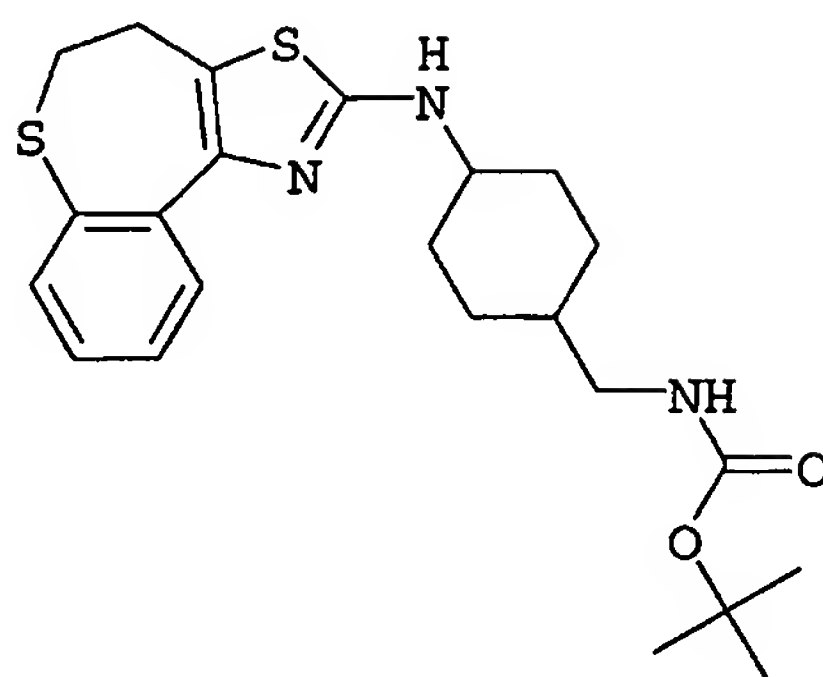
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In a further embodiment, the compound has the structure:



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In a still further embodiment, the compound has the structure:



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In the present invention as relates to tricyclic compounds, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more heteroatoms such as oxygen, sulfur, and nitrogen. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinoliziny, and 2,1,3-benzothiazolyl. Furthermore, any of the heteroaryl groups recited above may be substituted with thienyl, isoxazolyl, or pyridyl.

25

Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are not limited to the acids and bases listed herein. The salts include, but are not limited to the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The salts include, but are not limited to the following organic acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The salts include, but are not limited to the inorganic base, ammonia. The salts include, but are not limited to the following organic bases: methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

20

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

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The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

This invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, the amount of the compound is an amount from about 0.01 mg to about 800 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 500 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 250 mg. In another embodiment, the amount of the compound is an amount from about 0.1 mg to about 60 mg. In another embodiment, the amount of the compound is an amount from about 1 mg to about 20 mg. In a further embodiment, the carrier is a liquid and the composition is a solution. In another embodiment, the carrier is a solid and the composition is a tablet. In a further embodiment, the carrier is a gel and the composition is a suppository.

This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

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This invention provides a use of a compound of this invention for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human Y5 receptor. In different embodiments, the abnormality is an eating disorder, obesity, bulimia nervosa, a sexual disorder, a reproductive disorder, depression, an epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, or a sleep disturbance.

In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease.

In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants,

solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and

isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for treating the above noted disorders.

This invention further provides compositions which need not be pharmaceutical as that term is understood in the art. Such compositions comprise a compound in accordance with the subject invention in an amount effective to agonize and/or antagonize a Y5 receptor and a suitable carrier.

Still further, the invention provides a method of agonizing and/or antagonizing a Y5 receptor which comprises contacting the receptor, e.g. in vitro or in vivo, with an amount of a compound of this invention effective to agonize and/or antagonize the receptor.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details and ResultsI. Synthetic Methods for ExamplesA. Tricyclic Compounds

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General Procedures Relating to Examples:

For the formation of 2-aminothiazoles from 2-haloketones and thioureas, see, for example, Kearney, P.C., et al., 1998; Di Fabio, R. and Pentassuglia, G., 1998; De Kimpe, N., et al., 1996; Plazzi, P.V., et al., 1995; and Novikova, A. P., 1991.

For the formation of thiazoles from 2-haloketones and thioamides, see, for example, Critcher, D. J. and Pattenden, G., 1996; and Friedman, B. S., et al., 1937.

For the formation of 2-aminoimidazoles from 2-haloketones and guanidines, see, for example, Little, T. L. and Webber, 1994; and Chabaka, L.M., et al., 1994.

For the formation of imidazoles from 2-haloketones and amidines, see, for example, Demchenko, A. M., et al., 1997; and Nagao, Y., et al., 1996.

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For the synthesis of 2-aminooxazoles from 2-haloketones and ureas, see, for example, Pathak, V.N., et al., 1993; Crangk, G. and Foulis, M.J., 1971; and Marchetti, E., et al., 1968.

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For the formation of oxazoles from 2-haloketones and amides, see, for example, Hammar, W.J. and Rustad, M.A., 1981; and Zhao, Z., et al., 1991.

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All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. Examples 1-90 described in this patent application were named using ACD/Name program (version 2.51, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

^1H and ^{13}C spectra were recorded at 300 and 75 MHz (QE Plus) with CDCl_3 as solvent (unless otherwise noted) and tetramethylsilane as internal standard. s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sextet; septet; b = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Low-resolution electrospray MS spectra were measured (ESMS, MS) and MH^+ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). Melting points were determined in open capillary tubes on a Med-Temp apparatus and are uncorrected.

General Procedure for the Synthesis of Bromoketones:

To a cooled solution of the ketone (1 equivalent) in acetic acid was slowly added bromine (1 equivalent). The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated and the residue

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dissolved in dichloromethane, washed with saturated sodium bicarbonate and water. The organic phase was dried over sodium sulfate. Evaporation of the combined decolorized organic phase afforded a light yellow oil in > 80% yield in most cases.

Similarly, the following were prepared:

6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one was obtained as a light yellow oil in 97% yield from 8-fluoro 1-benzosuberone and bromine: ^1H NMR δ 7.30 (dd, 1H, $JJ = 2.7, 9.0$ Hz), 7.20-7.09 (m, 2H), 4.85 (dd, 1H, $JJ = 4.2, 7.5$ Hz), 3.06-2.97 (m, 1H), 2.91-2.81 (m, 1H), 2.43-2.24 (m, 2H), 2.05-1.97 (m, 2H).

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6-Bromo-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one was obtained as a light brown oil in 97% yield from 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one and bromine: ^1H NMR δ 7.68 (d, 1H, $J = 8.6$ Hz), 6.80 (dd, 1H, $J = 2.5, 8.6$ Hz), 6.70 (d, 1H, $J = 2.5$ Hz), 4.87 (dd, 1H, $J = 4.3, 7.9$ Hz), 3.85 (s, 3H), 3.10-2.99 (m, 1H), 2.94-2.82 (m, 1H), 2.40-2.30 (m, 2H), 2.0 (m, 2H).

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2-Methoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one: To a homogeneous mixture of phosphorus pentoxide and 85% phosphorus acid at 100 °C, was added 5-(3-methoxyphenyl)pentanoic acid in small portions over 20 minutes. The vigorously stirred mixture was heated at 100 °C for 6 hours. Then it was poured on ice-water, and extracted with ether (3 times). The organic phase was washed with water and dried over anhydrous sodium sulfate. Evaporation of the combined organic phase afforded a light yellow oil in more than 95% yield; ^1H NMR δ 7.77 (d,

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1H, $J = 8.6$ Hz), 6.80 (dd, 1H, $J = 2.5, 8.6$ Hz), 6.69 (d, 1H, $J = 2.5$ Hz), 3.84 (s, 3H), 2.90 (t, 2H, $J = 6.2$ Hz), 2.71 (t, 2H, $J = 5.9$ Hz), 1.91-1.76 (m, 4H).

5 5-(3-Methoxyphenyl)pentanoic acid. A mixture of ethyl 5-(3-methoxyphenyl)pentanoate (1 equivalent) and sodium hydroxide (3 equivalents) in THF/H₂O was heated at reflux overnight. THF was evaporated, the aqueous phase acidified with 6N HCl to pH < 5, and then extracted with a mixture
10 of chloroform : isopropyl alcohol (3 : 1, 5 times). The organic phase was dried over anhydrous sodium sulfate. A light yellow oil was obtained in more than 85% yield after removal of the solvent: ¹H NMR δ 7.20 (m, 1H), 6.79-6.73 (m, 3H), 3.80 (s, 3H), 2.62 (m, 2H), 2.38 (m, 2H), 1.68
15 (m, 4H).

Ethyl 5-(3-methoxyphenyl)pentanoate. A reaction mixture comprising ethyl (E) 5-(3-methoxyphenyl) 4-pentenoate and 5% palladium on carbon in methanol was stirred under 300
20 psi H₂ overnight. A light yellow oil was obtained after filtration and evaporation: ¹H NMR δ 7.20 (m, 1H), 6.78-6.72 (m, 3H), 4.12 (q, 2H, $J = 7.1$ Hz), 3.80 (s, 3H), 2.60 (m, 2H), 2.32 (m, 2H), 1.66 (m, 4H), 1.25 (t, 3H, $J = 7.1$ Hz).

25 Ethyl (E) 5-(3-methoxyphenyl) 4-pentenoate. To a refluxed solution of 3-iodoanisole (5.0 g, 21.37 mmol, 1 equivalent), tetrakis(triphenylphosphine)-palladium(0) ([C₆H₅)₃P]₄Pd, 740 mg, 0.64 mmol, 0.03 equivalent), and
30 triethyl amine (6.0 ml, 42.74 mmol, 2.0 equivalents) in CH₃CN/THF, was added 1.0 g of ethyl 4-pentenoate every two hours (total 3.3 g, 25.64 mmol, 1.2 equivalents). After the addition was complete, the reaction mixture was stirred at reflux overnight. Solvent was removed and the

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dark brown residue dissolved in 5% HCl and extracted with methylene chloride (3 times). The combined organic extracts were washed with saturated sodium bicarbonate. A dark brown oil was obtained after the organic solvent was removed. The crude product was purified by flash column (silica gel, chloroform : hexane = 1 : 5) to afford 3.6 g of a light yellow oil in 72% yield: ^1H NMR δ 7.21 (t, 1H, J = 7.9 Hz), 6.93 (m, 1H), 6.87 (m, 1H), 6.76 (dd, 1H, J = 2.6, 8.1 Hz), 6.40 (d, 1H, J = 18 Hz), 6.25-6.16 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 3.81 (s, 3H), 2.50 (m, 4H), 1.26 (t, 3H, J = 7.2 Hz).

4-Bromo-9-methoxy-3,4-dihydro-1-benzoxepin-5(2H)-one was obtained as a light yellow oil in 100% yield from 9-methoxy-3,4-dihydro-1-benzoxepin-5(2H)-one and bromine: ^1H NMR δ 7.32 (t, 1H, J = 4.8 Hz), 7.06 (d, 2H, J = 5.1 Hz), 4.99 (dd, 1H, J = 7.0, 8.4 Hz), 4.60-4.53 (m, 1H), 4.20-4.11 (m, 1H), 3.90 (s, 3H), 3.02-2.91 (m, 1H), 2.56-2.45 (m, 1H).

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9-Methoxy-3,4-dihydro-1-benzoxepin-5(2H)-one. To PPA in toluene at 100 °C, was added 4-(2-methoxyphenoxy)butanoic acid and the mixture stirred overnight. The mixture was poured onto ice-water, and extracted with ether (3 times). The combined organic phase was washed with water and dried over anhydrous sodium sulfate. Evaporation of the organic phase afforded a light yellow oil in 10% yield: ^1H NMR δ 7.33 (dd, 1H, J = 4.4, 5.1 Hz), 7.03 (d, 2H, J = 4.3 Hz), 4.31 (t, 2H, J = 6.6 Hz), 3.90 (s, 3H), 2.90 (t, 2H, J = 6.9 Hz), 2.22 (p, 2H, J = 6.8 Hz).

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4-(2-Methoxyphenoxy)butanoic acid. To the mixture of guaiacol (2-methoxyphenol, 1.0 equivalent) and γ -butyrolactone, cooled in an ice-water bath, was added

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potassium ethoxide in small portions. The reaction mixture was heated at 110 °C overnight, and then at 155 °C for an additional 10 hours. The mixture was then poured into ice water, basified to pH 9.5 with saturated sodium bicarbonate, and extracted with chloroform. The aqueous phase was separated, acidified to pH 2.5 with 2N HCl, and extracted with a mixture of chloroform : isopropyl alcohol (3 : 1). The organic phase was dried over anhydrous sodium sulfate and evaporated to afford 4-(2-methoxyphenoxy)butanoic acid as a light brown oil in 55% yield. The crude product was used for next reaction without further purification: ¹H NMR δ 6.90 (m, 4H), 4.08 (t, 2H, *J* = 6.2 Hz), 3.85 (s, 3H), 2.62 (t, 2H, *J* = 7.2 Hz), 2.16 (p, 2H, *J* = 6.6 Hz).

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3-Bromo-2,3-dihydro-4*H*-chromen-4-one was obtained as a yellow oil in 100% yield from 4-chromanone and bromine. ¹H NMR δ 7.93 (dd, 1H, *J* = 1.5, 7.8 Hz), 7.53 (td, 1H, *J* = 1.8, 7.8 Hz), 7.11-7.04 (m, 2H), 4.64 (m, 3H).

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General Procedure for the Synthesis of Thioureas:

A protected diamine such as N-Boc-1,4-diaminobutane or N-Boc-1,5-diaminopentane (1 equivalent) was dissolved in tetrahydrofuran and stirred at room temperature. Benzoyl thioisocyanate (1 equivalent) was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 24 hours, and the solvent was removed under reduced pressure to afford a yellow oil.

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The yellow oil (1 equivalent) was then dissolved in methanol, an aqueous potassium carbonate (3 equivalents) solution added, and the mixture stirred for 48 hours. Water was added to the reaction mixture which was then

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extracted with 2x75 ml ethyl acetate. The combined extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give the desired thiourea.

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tert-Butyl 5-[(aminocarbothioyl)amino]pentylcarbamate was obtained as a light yellow wax from *tert*-butyl 5-[[(benzoylamino)carbothioyl]amino]-pentylcarbamate. ¹H NMR (CD₃OD) δ 3.44 (m, 1H), 3.10 (m, 1H), 3.01 (t, 2H, *J* = 6.7 Hz), 1.60-1.31 (m, 6H), 1.41 (s, 9H); 262 (ESMS, MH⁺).

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tert-Butyl 5-[[(benzoylamino)carbothioyl]amino]-pentylcarbamate was obtained a light yellow solid in 79% yield from *N*-BOC-1,5-diaminopentate and benzoyl isothiocyanate; m.p. 90-93 °C; ¹H NMR δ (17001-131-1)

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tert-Butyl 4-[(aminocarbothioyl)amino]butylcarbamate was obtained as a light yellow wax from *tert*-butyl 4-[[(benzoylamino)carbothioyl]amino]-butylcarbamate. ¹H NMR (CD₃OD) δ 3.48 (m, 1H), 3.10 (m, 1H), 3.05 (t, 2H, *J* = 6.5 Hz), 1.60 (m, 4H), 1.42 (s, 9H); 248 (ESMS, MH⁺).

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tert-Butyl 4-[[(benzoylamino)carbothioyl]amino]-butylcarbamate was obtained as a light brown oil in 93% yield from *N*-BOC-1,4-diaminobutane and benzoyl isothiocyanate.

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trans-tert-Butyl-{4-[(aminocarbothioyl)amino]-cyclohexyl}methylcarbamate was obtained as a light yellow wax from *trans-tert*-butyl (4-[[(benzoylamino)carbothioyl]amino]cyclohexyl)-methylcarbamate. ¹H NMR (CD₃OD) δ 3.92 (m, 1H), 2.86 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.37 (m, 1H), 1.06 (m, 4H); 288 (ESMS, MH⁺).

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trans-tert-Butyl (4-{[(benzoylamino)carbothioyl]-amino}cyclohexyl)-methylcarbamate was obtained as a yellow solid in 97% yield from tert-butyl 4-aminocyclohexylmethylcarbamate and benzoyl isothiocyanate.

trans-tert-Butyl 4-aminocyclohexylmethylcarbamate was obtained in more than 95 % yield by hydrogenation of benzyl 4-{[(tert-butoxycarbonyl)amino]methyl} cyclocarbamate.

Benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate: To a stirred suspension of 4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexanecarboxylic acid (Maybridge Chemical Co., Ltd.) (45g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) was added triethylamine (32 ml) over a period of 20 min whilst maintaining the internal temperature at -10-0 C. The mixture was slowly warmed and then stirred at 70 C for 4 h. After cooling to 40 C, benzyl alcohol (36 ml) was added and the reaction mixture heated at reflux for 20 h. The cold reaction mixture was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallization of the organic residue from ethyl acetate and diethyl ether gave the title compound, benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate as a white solid, m.p. 129-131 C.

trans-tert-Butyl {4-[(aminocarbothioyl)amino]cyclohexyl}carbamate was obtained as a yellow solid from trans-tert-Butyl 4-(benzoylamino)carbothioylamino}cyclohexyl)-carbamate: ¹H NMR (CD₃OD) δ 3.94 (m, 1H),

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3.30 (m, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 1.41 (s, 9H),
1.26 (m, 4H); 274 (ESMS, MH⁺).

5 *trans*-*tert*-Butyl-4-{[(benzoylamino)carbothioyl]-
amino}cyclohexyl)carbamate was obtained as a white solid
in 66% yield from *tert*-butyl 4-aminocyclohexylcarbamate
and benzoyl isothiocyanate.

10 *trans*-*tert*-Butyl 4-aminocyclohexylcarbamate was obtained
as a light yellow wax in more than 95% yield by
hydrogenation of benzyl 4-[(*tert*-butoxycarbonyl)-
amino]cyclohexylcarbamate.

15 *trans*-Benzyl 4-{[(aminocarbothioyl)amino]methyl}
cyclohexylcarbamate was obtained as a yellow solid in 71%
yield from *trans*-Benzyl-4-{[(Benzoylamino) carbothioyl]-
amino}methyl)-cyclohexylcarbamate; 322 (ESMS, MH⁺).

20 *trans*-Benzyl-4-({[(benzoylamino)carbothioyl]-
amino}methyl)-cyclohexylcarbamate was obtained as a yellow
solid from benzyl 4-(aminomethyl)cyclohexylcarbamate and
benzoyl isothiocyanate.

25 *trans*-Benzyl 4-(aminomethyl)cyclohexylcarbamate was
obtained as a white solid in more than 95% yield by
stirring benzyl-4-{[(*tert*-butoxycarbonyl)amino]-
methyl}cyclohexylcarbamate in 2N HCl (made from 1 : 1 of EtOAc
and 4N HCl in dioxane).

30 **General Procedure for the Synthesis of Tricyclic
Thiazoles:**

A mixture of a bromoketone such as 6-bromo-3-fluoro-
6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (1.2

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equivalent), thiourea (1 equivalent), and diisopropylethylamine (2 equivalents) in anhydrous ethanol was stirred and heated at reflux overnight. The solvent was evaporated and the brown residue dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane three times. The combined extracts were dried over anhydrous sodium sulfate and the solvent removed to afford a crude product which was purified by flash column chromatography (silica gel).

General Procedure for the Deprotection of BOC-Protected Amines:

The Boc protected amine was dissolved in Et₂O. The same volume of 4N HCl in dioxane was added to make a 2N solution of HCl. The reaction mixture was stirred at room temperature overnight, and the solvent removed under reduced pressure to afford the desired product as its HCl salt.

tert-Butyl-5-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-yl)amino]-pentylcarbamate was obtained as a light yellow oil in 80% yield from 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one and *tert*-butyl 5-[(aminocarbothioyl)amino]-pentylcarbamate: ¹H NMR δ 7.70 (dd, 1H, *J* = 2.7, 10.8 Hz), 7.05 (dd, 1H, *J* = 6.0, 8.4 Hz), 6.83 (td, 1H, *J* = 2.7, 8.4 Hz), 5.12 (m, 1H), 4.53 (m, 1H), 3.26 (q, 2H, *J* = 5.7 Hz), 3.14 (m, 2H), 2.89 (t, 2H, *J* = 6.9 Hz), 2.79 (m, 2H), 2.09 (m, 2H), 1.68 (m, 4H), 1.50 (m, 2H), 1.44 (s, 9H); 420 (ESMS, MH⁺).

N-(5-Aminopentyl)-*N*-(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amine dihydrogen chloride was obtained as a yellow solid in more than 95% yield from deprotection of tert-butyl 5-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amino]pentylcarbamate by using 2N HCl (made from 1 : 1 of ethyl acetate and 4N HCl in dioxane); ¹H NMR (CD₃OD) δ 7.38-7.31 (m, 2H), 7.10 (td, 1H, *J* = 2.4, 8.4 Hz), 3.71 (m, 2H), 3.49 (t, 2H, *J* = 6.9 Hz), 2.95 (m, 2H), 2.78 (m, 2H), 2.17 (m, 2H), 1.85-1.68 (m, 4H), 1.54 (m, 2H); 320 (ESMS, MH⁺).

tert-Butyl-4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amino]-butylcarbamate was obtained as a yellow oil in 31% yield from 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one and tert-butyl 4-[(aminocarbothioyl)amino]-butylcarbamate: ¹H NMR δ 7.70 (dd, 1H, *J* = 3.0, 10.8 Hz), 7.05 (dd, 1H, *J* = 6.0, 8.4 Hz), 6.82 (td, 1H, *J* = 3.0, 8.3 Hz), 5.14 (m, 1H), 4.59 (m, 1H), 3.30 (m, 2H), 3.18 (m, 2H), 2.86 (t, 2H, *J* = 6.9 Hz), 2.79 (m, 2H), 2.10 (m, 2H), 1.74-1.53 (m, 4H), 1.44 (s, 9H).

N-(4-Aminobutyl)-*N*-(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amine hydrogen chloride was obtained as a yellow solid in more than 95% yield by deprotection of tert-butyl 4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amino]butylcarbamate with 2N HCl (made from 1 : 1 of 4N HCl in dioxane and ethyl acetate): ¹H NMR (CD₃OD) δ 7.39-7.31 (m, 2H), 7.10 (td, 1H, *J* = 3.0, 8.4 Hz), 3.54 (m, 2H), 2.97 (m, 2H), 2.79 (m, 4H), 2.18 (m, 2H), 1.83 (m, 4H). (no MS).

trans-*tert*-Butyl-{4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-[1,2-*d*][1,3]thiazol-2-yl)amino]cyclohexyl}methylcarbamate was obtained as a yellow oil in 80% yield from 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one and *trans*-*tert*-butyl {4-[(aminocarbothioyl)-amino]cyclohexyl}methylcarbamate: ¹H NMR δ 7.69 (dd, 1H, *J* = 2.8, 10.8 Hz), 7.05 (dd, 1H, *J* = 5.9, 8.4 Hz), 6.82 (td, 1H, *J* = 2.7, 8.3 Hz), 4.87 (m, 1H), 4.61 (m, 1H), 3.28 (m, 1H), 3.00 (m, 1H), 2.85 (t, 2H, *J* = 6.9 Hz), 2.79 (m, 2H), 2.22 (m, 2H), 2.08 (m, 2H), 1.85 (m, 2H), 1.74 (m, 1H), 1.44 (s, 9H), 1.45-1.02 (m, 4H); 446 (ESMS, MH⁺).

N-(4-Aminomethyl)cyclohexyl]-*N*-(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amine hydrogen chloride was obtained as a yellow solid in more than 95% yield by deprotection of *tert*-butyl {4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazol-2-yl)amino]cyclohexyl}methylcarbamate: ¹H NMR (CD₃OD) δ 7.34 (td, 2H, *J* = 2.7, 9.6 Hz), 7.11 (m, 1H), 3.61 (m, 1H), 2.82-2.76 (m, 6H), 2.18 (m, 4H), 1.96 (m, 2H), 1.69 (m, 1H), 1.50 (m, 2H), 1.24 (m, 2H); 346 (ESMS, MH⁺).

trans-*tert*-Butyl-4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-[1,2-*d*][1,3]thiazol-2-yl)amino]cyclohexylcarbamate was obtained as a yellow solid in 59% yield from 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one and *trans*-*tert*-butyl {4-[(aminocarbothioyl)-amino]cyclohexyl}-carbamate: ¹H NMR δ 7.69 (dd, 1H, *J* = 2.7, 10.8 Hz), 7.04 (dd, 1H, *J* = 6.0, 8.1 Hz), 6.82 (td, 1H, *J* = 2.7, 8.2 Hz), 4.95 (m, 1H), 4.45 (m, 1H), 3.39 (m, 2H), 2.84 (t, 2H, *J* = 6.9 Hz),

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2.77 (m, 2H), 2.10 (m, 2H), 2.07 (m, 4H), 1.44 (s, 9H),
1.28 (m, 4H); 432 (ESMS, MH⁺).

5 N-(4-Aminocyclohexyl)-N-(9-fluoro-5,6-dihydro-4H-
benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-yl)amine
hydrogen chloride was obtained as a yellow solid in more
than 95% yield by deprotection of tert-butyl 4-[(9-
fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-
10 d][1,3]thiazol-2-yl)amino]-cyclohexylcarbamate with 2N HCl
(made from 1 : 1 of ethyl acetate and 4N HCl in dioxane):
¹H NMR (CD₃OD) δ 7.35 (m, 2H), 7.12 (m, 1H), 3.68 (m, 1H),
3.17 (m, 1H), 2.76 (m, 4H), 2.25-2.13 (m, 6H), 1.59 (m,
4H); 332 (ESMS, MH⁺).

15 trans-tert-Butyl-{4-[(8-Methoxy-5,6-dihydro-4H-
benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-yl)amino]-
cyclohexyl}methylcarbamate was obtained as a light yellow
oil in 46% yield from 6-bromo-2-methoxy-6,7,8,9-
tetrahydro-5H-benzo[a]cyclohepten-5-one and trans-tert-
20 butyl-{4-[(aminocarbothioyl)amino]-
cyclohexyl}methylcarbamate; 458 (ESMS, MH⁺).

N-[4-(Aminomethyl)cyclohexyl]-8-methoxy-5,6-dihydro-4H-
benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-amine hydrogen
25 chloride was obtained as a yellow solid in more than 95%
yield by deprotection of trans-tert-butyl-{4-[(8-methoxy-
5,6-dihydro-4H-benzo[6,7]-cyclohepta[1,2-d][1,3]thiazol-2-
yl)amino]cyclohexyl}-methylcarbamate) with 2N HCl (made
from 1 : 1 of ethyl acetate and 4N HCl in dioxane): ¹H NMR
30 (CD₃OD) δ 7.48 (m, 1H), 6.91 (m, 2H), 3.81 (s, 3H), 3.54
(m, 1H), 2.83-2.70 (m, 6H), 2.10 (m, 4H), 1.95 (m, 2H),
1.70 (m, 1H), 1.50 (m, 2H), 1.24 (m, 2H); 358 (ESMS, MH⁺).

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Benzyl-{4-[(8-Methoxy-5,6-dihydro-4H-benzo[6,7]-cyclohepta[1,2-d][1,3]thiazol-2-yl)amino]methyl}-cyclohexylcarbamate was obtained as a light yellow oil in 60% yield from 6-bromo-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one and trans-benzyl-4-{[(aminocarbothioyl)amino]methyl}-cyclohexylcarbamate: ¹H NMR δ 7.88 (d, 1H, J = 8.6 Hz), 7.35 (m, 5H), 6.79 (dd, 1H, J = 2.4, 8.8 Hz), 6.68 (d, 1H, J = 2.6 Hz), 5.30 (m, 1H), 5.08 (s, 2H), 4.62 (m, 1H), 3.81 (s, 3H), 3.45 (m, 1H), 3.08 (m, 2H), 2.83 (t, 2H, J = 7.0 Hz), 2.77 (m, 2H), 2.08 (m, 4H), 1.85 (m, 2H), 1.55 (m, 1H), 1.10 (m, 4H); 492 (ESMS, MH⁺).

N-[4-(Aminocyclohexyl)methyl]-8-methoxy-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-amine trifluoroacetic acid salt was obtained as a brown syrup in more than 95% yield by refluxing benzyl {4-[(8-methoxy-5,6-dihydro-4H-benzo[6,7]cyclohepta[1,2-d][1,3]thiazol-2-yl)amino]methyl}cyclohexylcarbamate in TFA/H₂O (95 : 5) for 1 hour: ¹H NMR (CD₃OD) δ 7.47 (d, 1H, J = 8.4 Hz), 6.86 (m, 2H), 3.80 (s, 3H), 3.28 (m, 2H), 3.07 (m, 1H), 2.79-2.73 (m, 4H), 2.17-2.05 (m, 4H), 1.97 (m, 2H), 1.75 (m, 1H), 1.42 (m, 2H), 1.23 (m, 2H); 358 (ESMS, MH⁺).

tert-Butyl {4-[(7-Methoxy-4,5-dihydro[1]benzoxepino-[5,4-d][1,3]thiazol-2-yl)amino]cyclohexyl}methyl-carbamate was obtained as a light yellow oil in 69 % yield from 4-bromo-9-methoxy-3,4-dihydro-1-benzoxepin-5(2H)-one and trans-tert-butyl {4-[(aminocarbothioyl)amino]cyclohexyl}methylcarbamate: ¹H NMR δ 7.85 (dd, 1H, J = 1.5, 8.2 Hz), 7.02 (t, 1H, J = 8.1 Hz), 6.81 (dd, 1H, J = 1.4, 8.0 Hz), 4.83 (m, 1H), 4.60 (m, 1H), 4.40 (t, 2H, J = 5.1 Hz), 3.88 (s, 3H), 3.29 (m,

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1H), 3.18 (t, 2H, $J = 5.1$ Hz), 3.00 (m, 2H), 2.24 (m, 2H), 1.85 (m, 2H), 1.60 (m, 1H), 1.45 (s, 9H); 460 (ESMS, MH^+).

5 N-[4-(Aminomethyl)cyclohexyl]-7-methoxy-4,5-dihydro-[1]-
benzoxepino[5,4-d][1,3]thiazol-2-amine hydrogen chloride
was obtained as a yellow solid in more than 95% yield by
stirring tert-butyl {4-[(7-methoxy-4,5-
dihydro[1]benzoxepino[5,4-d][1,3]thiazol-2-
10 yl)amino]cyclohexyl}methylcarbamate in 2N HCl (made from 1
: 1 of ethyl acetate and 4N HCl in dioxane) for 3hr: 1H NMR
(CD_3OD) δ 7.25 (m, 1H), 7.20-7.06 (m, 2H), 4.32 (m, 2H),
3.85 (s, 3H), 3.56 (m, 1H), 3.19 (m, 2H), 2.86 (m, 2H),
2.21 (m, 2H), 1.94 (m, 2H), 1.73 (m, 1H), 1.55 (m, 2H),
15 1.27 (m, 2H); 360 (ESMS, MH^+).

tert-Butyl {4-(4H-Chromeno[4,3-d][1,3]thiazol-2-
yamino)cyclohexyl}-methylcarbamate was obtained as a
light yellow oil from 3-Bromo-2,3-dihydro-4H-chromen-4-
20 one and trans-tert-butyl {4-
[(aminocarbothioyl)amino]cyclohexyl}methylcarbamate: 1H NMR
 δ 7.58 (dd, 1H, $J = 1.5, 7.5$ Hz), 7.12 (m, 1H), 6.96 (m,
1H), 6.87 (dd, 1H, $J = 0.6, 8.1$ Hz), 5.07 (m, 1H), 4.60
(m, 1H), 3.29 (m, 1H), 3.00 (m, 2H), 2.07 (m, 2H), 1.85
25 (m, 2H), 1.50 (m, 1H), 1.45 (s, 9H), 1.25 (m, 2H), 1.05
(m, 2H); 416 (ESMS, MH^+).

N-[4-(Aminomethyl)cyclohexyl]-4H-chromeno[4,3-
d][1,3]thiazol-2-amine hydrogen chloride was obtained as a
30 yellow solid in more than 95% yield by stirring tert-butyl
[4-(4H-chromeno[4,3-d][1,3]thiazol-2-
yamino)cyclohexyl]methylcarbamate in 2N HCl (made from 1
: 1 of ethyl acetate and 4N HCl in dioxane) for 3hr: 1H NMR
(CD_3OD) δ 7.65 (dd, 1H, $J = 1.3, 7.8$ Hz), 7.29 (td, 1H, $J =$

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1.5, 7.8 Hz), 7.06 (td, 1H, $J = 1.0, 7.7$ Hz), 6.97 (dd, 1H, $J = 0.9, 8.4$ Hz), 5.23 (s, 2H), 3.73 (m, 1H), 2.84 (m, 2H), 2.21 (m, 2H), 1.95 (m, 2H), 1.70 (m, 1H), 1.50 (m, 2H), 1.25 (m, 2H); 316 (ESMS, MH^+).

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trans-N2-(4-(2-Methoxyethoxycarbonyl)aminomethyl)-cyclohexyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta-[d][1,3]-thiazol-2-amine:

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a. *t*-Butyl-*trans*-N-(4-(Benzoylamino-carbothioylamino)-cyclohexyl)methyl-carbamate: A solution of *t*-butyl *trans*-N-(4-aminocyclohexyl)methylcarbamate (4.683g, 20.51mmol) and benzoylisothiocyanate (3.77g, 23.1mmol) in THF (180 mL) was stirred at room temperature for 20 hours. The solvent was removed *in vacuo* to yield a golden viscous oil. The oil was triturated with hexane (250 mL) and the resulting solid was collected by filtration and washed with hexane to yield 91% (7.32g) of the product as an off-white solid: 1H NMR ($CDCl_3$) δ 1.20 (6H, m), 1.44 (9H, s), 1.83 (2H, m), 2.25 (2H, m), 3.01 (2H, t, $J = 6.4$ Hz), 4.20 (1H, m), 4.62 (1H, m), 7.51 (2H, t, $J = 7.9$ Hz), 7.60 (1H, t, $J = 7.4$ Hz), 7.81 (2H, d, $J = 7.2$ Hz), 8.93 (1H, s); 392 (ESMS, MH^+).

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b. *t*-Butyl *trans*-N-(4-(aminocarbothioylamino)-cyclohexyl)methylcarbamate: To a solution of *t*-butyl *trans*-N-(4-(benzoylamino-carbothioylamino)cyclohexyl)-methylcarbamate (7.30g, 18.6mmol) in MeOH (110 mL) was added a solution of potassium carbonate (5.15 g, 37.3 mmol) in water (50 mL). The solution was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue was extracted several times with EtOH. The combined EtOH extracts were evaporated to dryness to yield 6.15g of an off-white solid. The solid

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was dissolved in acetone (200 mL) and stirred for 20 minutes. The solution was filtered by suction to remove any insoluble salts and the filtrate evaporated to yield 98% (5.23 g) of the desired product as a slightly yellow solid: ^1H NMR (CDCl_3) δ 1.10 (6H, m), 1.43 (9H, s), 1.80 (2H, m), 2.10 (2H, m), 2.95 (2H, t, $J = 6.4$ Hz), 4.75 (1H, broad), 6.03 (2H, s), 6.64 (1H, broad); 288 (ESMS, MH^+).

c. 6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]-cyclohepten-5-one: To a solution of 8-fluoro-1-benzosuberone (20.00 g, 112.2 mmol) in glacial acetic acid (125 ml) was added bromine (5.8 mL, 112.6 mmol) dropwise. After addition was complete, the solution was poured into water (400 ml) and extracted with EtOAc (500 ml). The EtOAc layer was separated and washed with water (500 ml). The organic layer was dried over MgSO_4 , filtered and evaporated to yield 100% (28.9g) of the desired product as a viscous oil: ^1H NMR (CDCl_3) δ 2.00 (2H, m), 2.33 (2H, m), 2.84 (1H, m), 3.00 (1H, m), 4.83 (1H, m), 7.13 (2H, m), 7.29 (1H, dd).

d. *t*-Butyl *trans*-N-(4-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-ylamino)-cyclohexyl)methylcarbamate: A solution of *t*-butyl *trans*-N-(4-(aminocarbothioylamino)cyclohexyl)-methylcarbamate (22.4g, 78.0 mmol), 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (20.05g, 78.0 mmol) and *N,N*-diisopropylethylamine (22.5 ml) in absolute ethanol (260 ml) was heated at reflux for 3 hours. The solvent was removed in vacuo, and the resulting viscous golden oil was taken up in EtOAc (400 ml) and washed with water (600 ml). The EtOAc layer was separated and evaporated to yield 39.0 g of a viscous golden oil. The oil was chromatographed over silica gel eluting with EtOAc to yield 34.5g of the

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desired product (99% yield): ^1H NMR (CDCl_3) δ 1.18 (6H, h, $J = 12.2$ Hz), 1.44 (9H, s), 1.81 (2H, m), 2.22 (2H, m), 2.79 (2H, m), 2.86 (2H, t, $J = 7.1$ Hz), 3.00 (2H, t, $J = 6.3$ Hz), 3.25 (1H, broad), 4.62 (1H, broad), 4.86 (1H, broad), 6.83 (1H, dt, $J = 2.9$ Hz), 7.04 (1H, m), 7.70 (1H, dd, $J = 2.8$ Hz).

e. *trans*-N2-(4-Aminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine hydrochloride: A solution of *t*-butyl *trans*-N-(4-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-ylamino)cyclohexyl)-methylcarbamate (34.5g, 77.0 mmol) in EtOAc (200 ml) and 4N HCl in dioxane (100 ml) was stirred at room temperature for 2 hours. The resulting solid was collected by filtration, washed with Et_2O and dried under vacuum to yield 25.9g of the desired product as a slightly yellow solid. An additional 1.43g of the product was obtained by allowing the filtrate to stand in a closed flask for several days. The overall yield was 85%: ESMS $m/e = 346$ (MH^+); ^1H NMR (CD_3OD) δ 1.25 (2H, m), 1.51 (2H, m), 1.70 (1H, broad), 1.95 (2H, m), 2.18 (4H, m), 2.80 (6H, m), 3.63 (1H, broad), 7.11 (1H, dt, $J = 2.5\text{Hz}, 8.4$ Hz), 7.36 (2H, m).

f. *trans*-N2-(4-(2-Methoxyethoxycarbonyl)aminomethyl)-cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine: A solution of *trans*-N2-(4-aminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine hydrochloride (0.30 g, 0.72 mmol) and triethylamine (1.0 ml) in anhydrous THF (3 ml) was treated dropwise with chloroformic acid 2-methoxyethyl ester (0.114 g, 0.82 mmol). The solution was stirred at room temperature for 2 hours. The solvent was removed in vacuo and the residue

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chromatographed over silica gel eluting with 1:1 EtOAc/Hexane to yield the desired product (80 mg, 25% yield) as a highly viscous colorless oil: 448 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 1.11 (4H, h, $J = 9.8$ Hz), 1.42 (1H, broad), 1.80 (2H, m), 2.04 (2H, m), 2.20 (2H, m), 2.77 (2H, m), 2.84 (2H, t, $J = 6.9$ Hz), 3.04 (2H, t, $J = 6.4$ Hz), 3.24 (1H, broad), 3.38 (3H, s), 3.58 (2H, m), 4.22 (2H, m), 4.90 (1H, broad), 5.00 (1H, d), 6.81 (1H, dt, $J = 2.8$ Hz), 7.03 (1H, m), 7.68 (1H, dd, $J = 2.7$ Hz, 10.9 Hz).

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Similarly prepared were:

*N*2-(5-Aminopent-1-yl)-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine hydrochloride: Yellow solid; m.p. 220 °C (dec.); 320 (ESMS, MH^+); 1H NMR (CD_3OD) δ 7.34 (m, 2H), 7.10 (td, 1H, $J = 2.4, 8.4$ Hz), 3.49 (t, 2H, $J = 7.0$ Hz), 2.95 (t, 2H, $J = 7.7$ Hz), 2.78 (m, 4H), 2.17 (m, 2H), 1.82-1.67 (m, 4H), 1.54 (m, 2H).

20 **General Procedure for the Derivatization of Amines with Carboxylic Acid and Sulfonic Acid Derivatives:**

An amine such as *N*-[4-(aminomethyl)cyclohexyl]-4*H*-chromeno[4,3-*d*][1,3]thiazol-2-amine (0.305 mmol) was dissolved in 2ml CH_2Cl_2 with 1-3 equivalents of diisopropylethylamine. The appropriate sulfonyl chloride, acid chloride, isocyanate or carbamyl chloride (1-3 equivalents) was then added dropwise. The reaction solution was stirred at room temperature for 1-3 days, quenched with water and washed with 10% $NaHCO_3$, extracted with EtOAc, and then dried over Na_2SO_4 . The crude product was purified using column chromatography or preparative TLC.

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General Procedure for the Formation of Formamides:

The following sequence for the preparation of formamides is typical:

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N2-[4-(aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine-tert-butyl N-(4-aminobenzyl)carbamate: To a stirred solution of 4-amino-benzylamine (7.5 g, 61.39 mmol) in anhydrous THF (100 ml) under N₂ was added, in portions, di-t-butyl dicarbonate (13.5 g, 61.9 mmol). The solution was stirred at room temperature under N₂ for 90 minutes. The solvent was removed in vacuo to yield 100% (13.7 g) of the Boc-protected amine as a white solid: m.p. 70-72°C. ¹H-NMR (CDCl₃) δ 1.43 (9H, s), 3.62 (2H, broad), 4.18 (2H, d), 4.77 (1H, broad), 6.63 (2H, d), 7.06 (2H, d).

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tert-butyl N-(4-{[(benzoylamino)carbothioyl]amino}-benzyl)carbamate: To a stirred solution of N2-[4-(aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine-tert-butyl N-(4-aminobenzyl)carbamate (6.00 g, 27.0 mmol) in anhydrous THF (50 ml) was added benzoylisothiocyanate (4.43 g, 27.0 mmol). The solution was stirred for 2 hours and the solvent removed in vacuo to yield 100% (10.4 g) of the protected thiourea as a yellow solid: m.p. 161-163°C. ¹H-NMR (CDCl₃) δ 1.45 (9H, s), 4.33 (2H, d), 4.85 (1H, broad), 7.34 (2H, d), 7.60 (5H, m), 7.90 (2H, d), 9.13 (1H, s), 12.58 (1H, s); 386 (ESMS, MH⁺).

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tert-butyl N-{4-[(aminocarbothioyl)amino]benzyl}-carbamate: To a stirred solution of tert-butyl N-(4-{[(benzoylamino)carbothioyl]amino}benzyl)carbamate 10.4 g,

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27.0 mmol) in MeOH (150 ml) (not completely dissolved) was added a solution of K_2CO_3 (8.5 g, 61.5 mmol) in circa. 15 ml water. The solution was stirred at room temperature for 24 hours and filtered to remove a white precipitate. The filtrate was evaporated in vacuo to yield 100% (7.6 g) of an off-white solid.

tert-butyl N-{4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclo-hepta[d][1,3]thiazol-2-yl)amino]benzyl}-carbamate:
A solution containing tert-butyl N-{4-[(aminocarbothioyl)amino]benzyl}carbamate (7.60 g, 27.0 mmol), 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (6.95 g, 27.0 mmol), and diisopropylethylamine (5.0 ml) in EtOH (60 ml) was heated at reflux for 2.5 hours. The solvent was removed in vacuo and the residue dissolved in EtOAc (125 ml). The resulting solution was filtered to remove the insoluble (i-pr)₂NEt•HBr. The filtrate was transferred to a 250 ml round bottom flask and 4N HCl in dioxane (35 ml) added with stirring. The solution was stirred for 90 minutes and filtered to collect the hydrochloride salt. The solid was washed with EtOAc and then with Et₂O. Upon drying, 86% (11.1 g) of the Boc-protected amine hydrochloride was obtained as a slightly yellow solid: ¹H-NMR (d₄-MeOH) δ 1.43 (9H, s), 2.18 (2H, m), 2.80 (4H, m), 4.25 (2H, s), 7.12 (1H, dt), 7.33 (2H, m), 7.43 (4H, s).

2-(4-aminomethyl)anilino-1-aza-9-fluoro-4,5-dihydro-3-thia-benzo[e]azulene: To a stirred solution of tert-butyl N-{4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]-thiazol-2-yl)amino]benzyl}-carbamate (11.1 g, 23.3 mmol) in MeOH (150 ml) (partially dissolved) was added 4N HCl in dioxane (40 ml). The solution was

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brought to a brief gentle reflux and the solvent was then removed in vacuo. The resulting solid was re-suspended in Et₂O, filtered and dried to yield 90% (9.25 g) of the product di-hydrochloride as a white solid: m.p. 236-239°C. ¹H-NMR (CDCl₃) δ 1.75 (2H, broad), 2.06 (2H, m), 2.77 (2H, m), 2.83 (2H, t), 3.79 (2H, s), 6.82 (1H, t), 7.04 (1H, m), 7.22 (4H, m), 7.79 (1H, dd), 8.8 (1H, broad); 340 (ESMS, MH⁺).

10 N1-{4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl)amino]benzyl}-2-methoxyacetamide: To a stirred solution of 2-(4-aminomethyl)anilino-1-aza-9-fluoro-4,5-dihydro-3-thia-benzo[e]azulene (1.50 g, 3.64 mmol) in anhydrous pyridine (10 ml) and
15 diisopropylethylamine (5.0 ml) was added methoxyacetyl chloride (0.40 ml, 4.38 mmol) dropwise. The solution was stirred overnight, poured into water (200 ml), and extracted with EtOAc (200 ml). The EtOAc extract was evaporated to yield 1.8 g of a viscous golden oil. The
20 oil was chromatographed on silica-gel eluting with EtOAc to yield 80% (1.2 g) of the desired product as a foam. The product was converted to its HCl salt in chloroform using 1M HCl in Et₂O: m.p. 175-178°C; ¹H-NMR (CDCl₃) δ 2.15 (2H, m), 2.86 (4H, m), 3.42 (3H, s), 3.96 (2H, s), 4.50
25 (2H, d, J = 6.1 Hz), 7.00 (1H, t), 7.18-7.40 (7H, m), 7.61 (1H, dd, J = 2.5 Hz, 9.5 Hz); 412 (ESMS, MH⁺).

N-{4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl)amino]benzyl}-N-isopropyl-formamide:

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N2-{4-[(isopropylamino)methyl]phenyl}-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: A solution of 2-(4-aminomethyl)anilino-1-aza-9-fluoro-4,5-dihydro-3-thia-benzo[e]azulene (free-base) (0.54 g, 1.59

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mmol), anhydrous THF (8 ml), anhydrous DMF (4 ml) and 2-iodopropane (1.4 g, 8.24 mmol) was heated to reflux for 1 hour. The solution was then stirred at room temperature overnight. TLC (95% EtOAc/5% 2M NH₃ in MeOH) indicated a major product ($R_f \sim 0.4$) and some starting material. The solution was poured into water (200 ml) and extracted with EtOAc. The EtOAc layer was evaporated to yield 99% (0.6 g) of the product as a viscous golden oil. ¹H NMR spectrum showed the presence of an isopropyl group (δ 1.08, CDCl₃) as a doublet. The amine was not purified before the next step.

1-aza-9-fluoro-4,5-dihydro-2-(4-(n-(2-propyl)-formamido)-methyl)anilino-3-thia-benzo[e]azulene: To a stirred solution of N2-{4-[(isopropylamino)methyl]phenyl}-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine (0.60 g, 1.57 mmol) in anhydrous THF (10 ml) was added 1H-benzotriazole-1-carboxaldehyde (0.245 g, 1.67 mmol). The solution was stirred for 30 minutes at room temperature, poured into 2N NaOH (60 ml) and extracted with EtOAc. The EtOAc layer was again washed with 2N NaOH (60 ml) and evaporated to yield 0.55 g of a viscous golden oil. The oil was chromatographed on silica-gel eluting with 40% EtOAc/ 60% hexane to yield 23% (0.15 g) of the desired product as a viscous colorless oil. The oil was converted to its HCl salt in chloroform with 1N HCl in Et₂O. Upon evaporation of solvent and trituration with Et₂O, 104 mg of the desired HCl salt was isolated: m.p. 180-183°C. ¹H-NMR (CDCl₃) δ 1.10 (1.5H, d, $J = 6.8$ Hz), 1.20 (4.5H, d, 6.3 Hz), 2.10 (2H, m), 2.78 (2H, m), 2.83 (2H, m), 3.72 (1H, h), 4.30 (0.5H, s), 4.51 (1.5H, s), 6.82 (1H, m), 7.18 (3H, m), 7.34 (2H, m), 7.76 (1H, d), 8.23 (0.25H, s), 8.39 (1.75H, broad s); 410 (ESMS, MH⁺).

Example 1

trans-N2-(4-Dimethylaminosulfonylaminoethyl)-cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]-
5 cyclohepta[d][1,3]thiazol-2-amine

a. trans-1-Aminocarbothioylamino-4-(dimethylaminosulfonyl-aminomethyl)-cyclohexane: 4-(Dimethylaminosulfonylamino-methyl)cyclohexylamine (500
10 mg, 2.12 mmol) was suspended in dry THF (8 mL), cooled in an ice water bath and treated dropwise with benzoylisothiocyanate (290 µL, 2.16 mmol). The yellow solution was stirred at room temperature overnight and then concentrated. The residual yellow solid was
15 dissolved in chloroform and flash chromatographed over silica gel (49 g) eluting with EtOAc/hexane (2:3) to give a yellow solid (490 mg, 58%). This solid was suspended in MeOH (4 ml), cooled in a water bath and treated with potassium carbonate (170 mg, 1.23 mmol) in water (3 ml).
20 The mixture was stirred at room temperature for 1 hour before more MeOH (2 ml) and water (1.5 ml) were added. After 3 hours, the organic solvent was evaporated and the aqueous layer extracted with dichloromethane and EtOAc. The combined extracts were dried (Na₂SO₄), filtered and
25 concentrated to give a white foam (378 mg).

b. trans-N2-(4-Dimethylaminosulfonylaminoethyl)-cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]-
cyclohepta[d][1,3]-thiazol-2-amine: 6-Bromo-3-fluoro-
30 6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (69 mg, 0.27 mmol) and trans-1-aminocarbothioylamino-4-(dimethylaminosulfonylaminoethyl)-cyclohexane (119 mg, 0.40 mmol) were dissolved in EtOH (4 mL) and heated at reflux overnight. The solvent was evaporated and the

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residue partitioned between EtOAc and potassium carbonate solution. The organic phase was dried (Na_2SO_4), filtered and concentrated to give a light orange oil (179 mg) which was flash chromatographed over silica gel (14 g) eluting with EtOAc/hexane (2:3) to afford a pale yellow foam (105 mg, 86%): m.p. 60-65 °C; 453 (ESMS, MH^+); ^1H NMR (CDCl_3) δ 1.15 (4H, m), 1.50 (1H, broad), 1.90 (2H, m), 2.07 (2H, m), 2.25 (2H, m), 2.80 (2H, m), 2.82 (6H, s), 2.86 (2H, t, $J = 6.9$ Hz), 2.94 (2H, t, $J = 6.6$ Hz), 3.33 (1H, broad), 4.18 (1H, m), 4.81 (1H, d, $J = 7.6$ Hz), 6.83 (1H, m), 7.06 (1H, dd, $J = 6.0, 8.3$ Hz), 7.69 (1H, dd, $J = 2.8, 10.8$ Hz).

Example 2

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1-Aza-9-fluoro-4,5-dihydro-2-{5-(dimethyl-aminosulfonyl-amino)pentyl}amino-3-thia-benzo[e]azulene: 86% yield; 427 (ESMS, MH^+); ^1H NMR (CDCl_3) δ 7.67 (dd, 1H, $J=10.8, 3.0$ Hz), 7.05 (dd, 1H, $J=6.0, 8.2$), 6.82 (apparent dt, 1H, $J=2.8, 8.3$ Hz), 5.74 (broad, 1H), 5.24 (t, 1H, $J=5.7$ Hz), 3.16 (q, 2H, $J=4.2$ Hz), 2.97 (q, 2H, $J=6.3$ Hz), 2.84 (t, 2H, $J=6.9$ Hz), 2.77 (s, 6H), 2.75 (masked m, 2H), 2.08 (m, 2H), 1.58 (p, 2H, $J=6.75$ Hz), 1.43 (p, 2H, $J=6.9$ Hz), 1.26 (p, 2H, $J=7.2$ Hz).

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Example 3

1-Aza-9-fluoro-2-(5-(2-fluorophenyl)sulfonylamino)-pentylamino-4,5-dihydro-3-thia-benzo[e]azulene was obtained as a yellow oil in 36% yield; ^1H NMR δ 7.89 (td, 1H, $J = 1.6, 7.5$ Hz), 7.62 (dd, 1H, $J = 2.7, 10.8$ Hz), 7.55 (m, 1H), 7.29-7.17 (m, 2H), 7.06 (dd, 1H, $J = 6.0, 8.1$ Hz), 6.81 (td, 1H, $J = 3.0, 8.2$ Hz), 5.44 (b, 2H), 3.16 (m, 2H), 2.95 (m, 2H), 2.84 (t, 2H, $J = 6.9$ Hz), 2.08

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(m, 2H), 1.58-1.25 (m, 6H); ⁹⁹ 478 (ESMS, MH⁺); ; m.p. (HCl salt) 55-57 °C.

Example 4

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1-Aza-9-fluoro-4,5-dihydro-2-(5-(1-naphthyl)sulfonyl-amino)-pentylamino-3-thia-benzo[e]azulene: was obtained as a yellow oil in 29% yield; ¹H NMR δ 8.69 (d, 1H, J = 8.7 Hz), 8.25 (dd, 1H, J = 0.9, 7.2 Hz), 8.05 (d, 1H, J = 8.4 Hz), 7.93 (d, 1H, J = 8.1 Hz), 7.68-7.49 (m, 4H), 7.04 (dd, 1H, J = 5.7, 8.1 Hz), 6.80 (td, 1H, J = 2.9, 8.1 Hz), 5.52 (b, 1H), 5.41 (b, 1H), 3.01 (m, 2H), 2.89-2.74 (m, 6H), 2.07 (m, 2H), 1.39-1.12 (m, 6H); 510 (ESMS, MH⁺).

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Example 5

1-Aza-9-fluoro-4,5-dihydro-2-(4-(methane-sulfonylamino)-butyl)amino-3-thia-benzo[e]azulene was obtained as a yellow oil in 59% yield: ¹H NMR δ 7.63 (dd, 1H, J = 2.7, 10.8 Hz), 7.07 (dd, 1H, J = 6.0, 8.4 Hz), 6.84 (td, 1H, J = 2.9, 8.4 Hz), 5.61 (b, 1H), 5.34 (b, 1H), 3.22 (m, 2H), 3.09 (m, 2H), 2.94 (s, 3H), 2.86-2.76 (m, 4H), 2.09 (m, 2H), 1.60 (m, 6H); 384 (ESMS, MH⁺).

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Example 6

1-Aza-9-fluoro-4,5-dihydro-2-(4-(dimethyl-aminosulfonyl-amino)butyl)amino-3-thia-benzo[e]-azulene was obtained as a yellow oil in 75% yield: ¹H NMR δ 7.65 (dd, 1H, J = 2.4, 10.8 Hz), 7.06 (t, 1H, J = 7.1 Hz), 6.83 (td, 1H, J = 2.7, 8.1 Hz), 5.57 (b, 1H), 5.05 (b, 1H), 3.21 (m, 2H), 3.02 (q, 2H, J = 5.7 Hz), 2.87-2.76 (m, 10H), 2.08 (m, 2H), 1.59 (m, 4H); 413 (ESMS, MH⁺).

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Example 7

1-Aza-9-fluoro-2-(4-(2-fluorophenyl)sulfonylamino)-
butylamino-4,5-dihydro-3-thia-benzo[e]azulene was obtained
5 as a light yellow oil in 81% yield: ^1H NMR δ 7.88 (td, 1H,
 $J = 1.5, 9.0$ Hz), 7.57 (m, 2H), 7.28-7.17 (m, 2H), 7.05
(dd, 1H, $J = 6.0, 8.1$ Hz), 6.81 (td, 1H, $J = 2.7, 8.1$ Hz),
5.64 (b, 2H), 3.14 (t, 2H, $J = 6.3$ Hz), 2.95 (t, 2H, $J =$
6.3 Hz), 2.83 (t, 2H, $J = 6.9$ Hz), 2.76 (m, 2H), 2.06 (m,
10 2H), 1.52 (m, 4H); 464 (ESMS, MH^+).

Example 8

1-Aza-9-fluoro-4,5-dihydro-2-(4-(1-naphthyl)sulfonyl-
15 amino)butylamino-3-thia-benzo[e]azulene was obtained as a
yellow oil in 78% yield: ^1H NMR δ 8.68 (d, 1H, $J = 8.4$ Hz),
8.24 (d, 1H, $J = 7.2$ Hz), 8.05 (d, 1H, $J = 8.4$ Hz), 7.93
(d, 1H, $J = 7.8$ Hz), 7.66-7.50 (m, 4H), 7.05 (dd, 1H, $J =$
6.0, 8.4 Hz), 6.80 (td, 1H, $J = 2.7, 8.1$ Hz), 5.62 (b,
20 1H), 5.39 (b, 1H), 3.02 (m, 2H), 2.87-2.74 (m, 6H), 2.07
(m, 2H), 1.41 (m, 4H); 496 (ESMS, MH^+).

Example 9

1-Aza-9-fluoro-4,5-dihydro-2-(4-((2(S)-methoxy-methyl)-
pyrrolidine-1-yl)sulfonyl)phenylamino-3-thia-
benzo[e]azulene was obtained as a light yellow solid in
72% yield: m.p. 186-188 $^{\circ}\text{C}$ ^1H NMR δ 7.94 (b, 1H), 7.76 (m,
3H), 7.57 (d, 2H, $J = 8.7$ Hz), 7.11 (dd, 1H, $J = 6.0, 8.4$
30 Hz), 3.75-3.64 (m, 2H), 3.45-3.32 (m, 2H), 3.38 (s, 3H),
3.11 (m, 1H), 2.94 (t, 2H, $J = 6.9$ Hz), 2.83 (m, 2H), 2.15
(m, 2H), 1.84 (m, 2H), 1.60 (m, 2H); 488 (ESMS, MH^+).
The hydrogen chloride salt was obtained as a yellow solid:
m.p. 151-155 $^{\circ}\text{C}$.

Example 10

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1-Aza-9-fluoro-4,5-dihydro-2-(5-(methylsulfonyl-amino)-
pentyl)amino-3-thia-benzo[e]azulene (hydrogen chloride
salt) was obtained as a yellow oil in 53% yield: ^1H NMR
(CD_3OD) δ 7.35 (dd, 1H, $J = 2.5, 9.9$ Hz), 7.28 (dd, 1H, $J =$
10 6.0, 8.4 Hz), 7.05 (td, 1H, $J = 2.5, 8.4$ Hz), 3.42 (t, 2H,
 $J = 7.0$ Hz), 3.06 (t, 2H, $J = 6.6$ Hz), 2.90 (s, 3H), 2.78
(t, 4H, $J = 7.1$ Hz), 2.14 (m, 2H), 1.74 (p, 2H, $J = 7.2$
Hz), 1.63-1.47 (m, 4H); 398 (ESMS, MH^+).

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Example 11

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(methyl-
sulfonylamino-methyl)cyclohexyl)amino-3-thia-
benzo[e]azulene: Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{FN}_3\text{O}_2\text{S}_2 + 0.25\text{H}_2\text{O}$: C,
20 56.12; H, 6.24; N, 9.82. Found: C, 56.15; H, 6.40; N,
9.52.

Example 12

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1-Aza-9-fluoro-4,5-dihydro-2-(5-(2,4-difluoro-
phenyl)sulfonylamino)pentylamino-3-thia-benzo[e]-azulene
(hydrogen chloride salt) was obtained as a yellow syrup in
83% yield: ^1H NMR (CD_3OD) δ 7.91 (m, 1H), 7.64 (dd, 1H, $J =$
2.8, 10.8 Hz), 7.08-6.92 (m, 3H), 6.82 (td, 1H, $J = 2.8,$
30 8.3 Hz), 5.23 (b, 2H), 3.21 (m, 2H), 2.97 (m, 2H), 2.86
(t, 2H, $J = 6.9$ Hz), 2.78 (m, 2H), 2.07 (m, 2H), 1.63-1.34
(m, 6H); 496 (ESMS, MH^+).

Example 13

1-Aza-9-fluoro-4,5-dihydro-2-(5-isopropyl-sulfonylamino)-
pentylamino-3-thia-benzo[e]azulene (hydrogen chloride
5 salt) was obtained as a yellow syrup in 12% yield: ^1H NMR
(free base) δ 7.69 (dd, 1H, J = 3.0, 10.8 Hz), 7.05 (dd,
1H, J = 5.9, 8.1 Hz), 6.82 (td, 1H, J = 2.8, 8.1 Hz), 5.34
(b, 1H), 3.92 (t, 1H, J = 6.0 Hz), 3.29-3.11 (m, 3H), 2.85
(t, 2H, J = 6.9 Hz), 2.79 (m, 2H), 2.10 (m, 2H), 1.80 (s,
10 3H), 1.73 (s, 3H), 1.64 (m, 4H), 1.44 (m, 2H).

Example 14

1-Aza-9-fluoro-4,5-dihydro-2-(5-(diethyl-aminosulfonyl-
15 amino)pentyl)amino-3-thia-benzo[e]-azulene (hydrogen
chloride salt) was obtained as a yellow syrup in 12%
yield: ^1H NMR (free base) δ 7.67 (dd, 1H, J = 2.7, 10.8
Hz), 7.06 (dd, 1H, J = 6.0, 8.3 Hz), 6.83 (td, 1H, J =
2.7, 8.3 Hz), 5.39 (b, 1H), 4.57 (t, 1H, J = 6.1 Hz), 3.24
20 (m, 6H), 2.95 (q, 2H, J = 6.7 Hz), 2.85 (t, 2H, J = 6.9
Hz), 2.79 (m, 2H), 2.08 (m, 2H), 1.60 (m, 2H), 1.50 (m,
2H), 1.39 (m, 2H), 1.08 (t, 6H, J = 7.1 Hz); 455 (ESMS,
MH $^+$).

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Example 15

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2-methoxy-5-methyl-
phenyl)sulfonylamino)pentylamino-3-thia-benzo[e]-azulene
(hydrogen chloride salt) was obtained as a yellow syrup in
30 80% yield: ^1H NMR (free base) δ 7.70 (m, 1H), 7.66 (dd, 1H,
 J = 2.9, 10.8 Hz), 7.31 (dd, 1H, J = 1.8, 8.4 Hz), 7.05
(dd, 1H, J = 6.0, 8.1), 6.91 (d, 1H, J = 8.4 Hz), 6.82
(td, 1H, J = 2.8, 8.3 Hz), 5.26 (m, 1H), 5.10 (t, 1H, J =
6.1 Hz), 3.93 (s, 3H), 3.18 (q, 2H, J = 5.7 Hz), 2.85 (m,

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4H), 2.78 (m, 2H), 2.33 (s, 3H), 2.09 (m, 2H), 1.58 (m, 2H), 1.48 (m, 2H), 1.34 (m, 2H); 504 (ESMS, MH⁺).

Example 16

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1-Aza-2-(5-benzylsulfonylamino)pentylamino-9-fluoro-4,5-dihydro-3-thia-benzo[e]azulene was obtained as a yellow oil in 68% yield: ¹H NMR δ 7.66 (dd, 1H, J = 2.7, 10.8 Hz), 7.38 (m 5H), 7.06 (dd, 1H, J = 6.0, 8.1 Hz), 6.84 (td, 1H, J = 2.9, 8.3 Hz), 5.21 (m, 1H), 4.62 (m, 1H), 4.24 (s, 2H), 3.21 (q, 2H, J = 6.2 Hz), 2.93 (q, 2H, J = 6.4 Hz), 2.85 (t, 2H, J = 6.9 Hz), 2.78 (m, 2H), 2.07 (m, 2H), 1.60 (m, 2H), 1.45 (m, 2H), 1.35 (m, 2H); 474 (ESMS, MH⁺).

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Example 17

1-Aza-2-(5-(3,4-difluorophenyl)sulfonylamino)-pentylamino-9-fluoro-4,5-dihydro-3-thia-benzo[e]-azulene was obtained as a yellow oil in 78% yield: ¹H NMR δ 7.73-7.61 (m, 2H), 7.56 (dd, 1H, J = 2.9, 10.8 Hz), 7.34-7.25 (m, 1H), 7.06 (dd, 1H, J = 2.9, 8.2 Hz), 6.82 (td, 1H, J = 2.8, 8.2 Hz), 5.42 (b, 1H), 5.34 (b, 1H), 3.19 (m, 2H), 2.92 (m, 2H), 2.86 (t, 2H, J = 7.0 Hz), 2.78 (m, 2H), 2.07 (m, 2H), 1.58 (m, 2H), 1.43 (m, 2H), 1.36 (m, 2H); 496 (ESMS, MH⁺). The hydrogen chloride salt was obtained as a tan solid: m.p. 68-70 °C.

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Example 18

1-Aza-9-fluoro-4,5-dihydro-2-(5-(4-methoxyphenyl)-sulfonylamino)pentylamino-3-thia-benzo[e]azulene was obtained as a yellow oil in 73% yield: ¹H NMR δ 7.79 (d, 2H, J = 9.0 Hz), 7.62 (dd, 1H, J = 2.9, 10.8 Hz), 7.06 (dd, 1H, J = 6.0, 8.4 Hz), 6.97 (d, 2H, J = 8.7 Hz), 6.82

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(td, 1H, $J = 2.8, 8.3$ Hz), 5.22 (m, 1H), 4.92 (m, 1H), 3.85 (s, 3H), 3.19 (q, 2H, $J = 5.7$ Hz), 2.91 (m, 2H), 2.86 (t, 2H, $J = 6.9$ Hz), 2.78 (m, 2H), 2.07 (m, 2H), 1.57 (p, 2H, $J = 7.2$ Hz), 1.45 (m, 2H), 1.36 (m, 2H); 490 (ESMS, MH⁺).

Example 19

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2-thienyl)-sulfonylamino)-pentylamino-3-thia-benzo[e]azulene was obtained as a light yellow solid in 70% yield: m.p. 152-154 °C; ¹H NMR δ 7.64-7.56 (m, 3H), 7.08 (m, 2H), 6.82 (td, 1H, $J = 2.8, 8.2$ Hz), 5.25 (b, 1H), 5.16 (b, 1H), 3.20 (m, 2H), 3.01 (m, 2H), 2.86 (t, 2H, $J = 6.9$ Hz), 2.77 (m, 2H), 2.07 (m, 2H), 1.58 (p, 2H, $J = 7.2$ Hz), 1.47 (m, 2H), 1.36 (m, 2H); 466 (ESMS, MH⁺).

Example 20

1-Aza-9-fluoro-2-(5-(2-trifluoroethyl)sulfonylamino)-pentylamino-4,5-dihydro-3-thia-benzo[e]azulene was obtained as a yellow oil in 25% yield: ¹H NMR δ 7.65 (dd, 1H, $J = 2.9, 10.8$ Hz), 7.07 (dd, 1H, $J = 5.9, 8.4$ Hz), 6.84 (td, 1H, $J = 2.9, 8.3$ Hz), 5.30 (b, 2H), 3.77 (q, 2H, $J = 9.1$ Hz), 3.25 (t, 2H, $J = 6.6$ Hz), 3.14 (t, 2H, $J = 6.6$ Hz), 2.85 (t, 2H, $J = 6.9$ Hz), 2.77 (m, 2H), 2.08 (m, 2H), 1.72-1.52 (m, 4H), 1.42 (m, 2H); 466 (ESMS, MH⁺).

Example 21

1-Aza-9-fluoro-2-(5-ethylsulfonylamino)pentylamino-4,5-dihydro-3-thia-benzo[e]azulene was obtained as a yellow oil in 72% yield: ¹H NMR δ 7.65 (dd, 1H, $J = 2.7, 10.8$ Hz), 7.06 (dd, 1H, $J = 6.0, 8.2$ Hz), 6.83 (td, 1H, $J = 3.0, 8.2$

105

Hz), 5.52 (m, 1H), 5.07 (m, 1H), 3.22 (m, 2H), 3.05 (m, 4H), 2.85 (t, 2H, $J = 7.0$ Hz), 2.77 (m, 2H), 2.05 (m, 2H), 1.60 (m, 2H), 1.51 (m, 2H), 1.38 (m, 5H); 412 (ESMS, MH^+).

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Example 22

1-Aza-2-(4-diethylaminosulfonylamino)butylamino-9-fluoro-4,5-dihydro-3-thia-benzo[e]azulene was obtained as a yellow oil in 36% yield: 1H NMR δ 7.68 (dd, 1H, $J = 2.7$, 10.8 Hz), 7.06 (dd, 1H, $J = 6.0$, 8.3 Hz), 6.84 (td, 1H, $J = 2.4$, 8.2 Hz), 5.18 (m, 1H), 4.36 (t, 1H, $J = 6.3$ Hz), 3.26 (m, 6H), 3.01 (q, 2H, $J = 6.5$ Hz), 2.86 (t, 2H, $J = 6.9$ Hz), 2.08 (m, 2H), 1.67 (m, 4H), 1.18 (t, 6H, $J = 7.1$ Hz).

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Example 23

1-Aza-9-fluoro-4,5-dihydro-2-(5-(1-methylimidazol-4-yl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene was obtained as a yellow solid in 74% yield: m.p. 50-53 °C; 1H NMR δ 7.66 (dd, 1H, $J = 2.7$, 10.8 Hz), 7.53 (s, 1H), 7.46 (s, 1H), 7.05 (dd, 1H, $J = 6.0$, 8.2 Hz), 6.82 (td, 1H, $J = 2.7$, 8.2 Hz), 5.96 (m, 1H), 5.47 (m, 1H), 3.71 (s, 3H), 3.18 (m, 2H), 2.96 (m, 2H), 2.85 (t, 2H, $J = 6.9$ Hz), 2.06 (m, 2H), 1.56 (m, 2H), 1.48 (m, 2H), 1.37 (m, 2H).

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Example 24

1-Aza-9-fluoro-4,5-dihydro-2-(5-(3,5-dimethyl-isoxazol-4-yl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene was obtained as a yellow oil in 80% yield: 1H NMR δ 7.63 (dd, 1H, $J = 2.7$, 10.8 Hz), 7.06 (dd, 6.0, 8.3 Hz), 6.83 (dd, 1H, $J = 2.8$, 8.2 Hz), 5.24 (b, 2H), 3.48 (m, 2H), 2.94 (m, 2H), 2.85 (t, 2H, $J = 7.0$ Hz), 2.77 (m, 2H), 2.63 (s, 3H),

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2.40 (s, 3H), 2.08 (m, 2H), ¹⁰⁶ 1.60 (p, 2H, $J = 7.5$ Hz),
1.49 (m, 2H), 1.38 (m, 2H).

Example 25

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1-Aza-9-fluoro-4,5-dihydro-2-(5-aminosulfonylamino)-
pentylamino-3-thia-benzo[e]azulene was obtained as a
yellow oil in 39% yield: ¹H NMR δ 7.58 (dd, 1H, $J = 2.7$,
10.8 Hz), 7.06 (dd, 1H, $J = 6.0$, 8.3 Hz), 6.82 (td, 1H, J
10 = 2.7, 8.2 Hz), 5.30 (b, 2H), 5.18 (b, 2H), 3.19 (t, 2H, J
= 6.4 Hz), 3.09 (m, 2H), 2.82 (t, 2H, $J = 5.4$ Hz), 2.76
(m, 2H), 2.07 (m, 2H), 1.85-1.47 (m, 4H), 1.43 (m, 2H).

Example 26

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trans-1-aza-9-fluoro-2-(4-(2-fluorophenyl)sulfonyl-amino-
methyl)cyclohexylamino-4,5-dihydro-3-thia-benzo[e]-
azulene: ¹H NMR δ 7.89 (apparent td, 1H, $J = 1.4$, 7.5 Hz),
7.62 (dd, 1H, $J = 2.7$, 10.8 Hz), 7.59 (m, 1H), 7.25-7.19
20 (m, 2H), 7.04 (dd, 1H, $J = 6.0$, 8.1 Hz), 6.81 (td, 1H, $J =$
3.0, 8.2 Hz), 5.08 (broad m, 1H), 4.95 (m, 1H), 3.02 (m,
1H), 2.90-2.75 (m, 6H), 2.25-0.80 (m, 10H).

Example 27

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trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(4-methoxy-phenyl)-
sulfonylaminomethyl}cyclohexylamino-3-thia-
benzo[e]azulene: 6.2% yield; ¹H NMR (CDCl₃) δ 7.79 (d, 2H,
 $J=8.7$ Hz), 7.62 (dd, 1H, $J=10.8$, 2.7 Hz), 7.05 (dd, 1H,
 $J=6.0$, 8.3 Hz), 6.98 (d, 2H, $J=8.7$ Hz), 6.82 (apparent dt,
30 1H, $J=2.8$, 8.2 Hz), 4.95 (d, 1H, $J=8$ Hz), 4.66 (t, 1H,
 $J=5.1$ Hz), 3.85 (s, 3H), 3.24 (b, 1H), 2.90-0.80 (m, 17H).

Example 28

trans-N²-(4-(2,6-Difluorophenylsulfonyl)aminomethyl)-
cyclohexyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta-
5 [d][1,3]-thiazol-2-amine: A solution of *trans*-N²-(4-
aminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]-
cyclohepta[d][1,3]thiazol-2-amine hydrochloride (200 mg,
0.52 mmol) and *N,N*-diisopropylethylamine (0.22 ml, 1.29
mmol) in dry THF (8 ml) was treated with 2,6-
10 difluorobenzenesulfonyl chloride (117 mg, 0.55 mmol) in
THF (2 ml). The mixture was stirred at room temperature
overnight. The solvent was evaporated. The residue was
dissolved in dichloromethane. The solution was then washed
with 5% HCl solution, dried (MgSO₄), filtered and
15 concentrated. The product was purified by preparative TLC
(EtOAc/hexane 1:1) to give a tan solid (53% yield): ¹H NMR
(CDCl₃) δ 1.10 (4H, m), 1.42 (1H, m), 1.80 (2H, m), 2.10
(2H, m), 2.20 (2H, m), 2.80 (2H, m), 2.84 (2H, t, *J* = 6.9
Hz), 2.92 (2H, m), 3.23 (1H, m), 5.05 (1H, broad), 5.55
20 (1H, broad), 6.80 (1H, m), 7.05 (3H, m), 7.50 (1H, m),
7.65 (1H, m)

Similarly prepared were:

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Example 29

trans-1-Aza-2-{4-benzylsulfonylaminomethyl}-
cyclohexylamino-9-fluoro-4,5-dihydro-3-thia-benzo[e]-
azulene: 23.6% yield; ¹H NMR (CDCl₃) δ 7.62 (dd, 1H,
30 *J*=10.8, 2.7 Hz), 7.50-7.20 (m, 5H), 7.05 (dd, 1H, *J*=6.0,
8.3 Hz), 6.81 (apparent dt, 1H, *J*=2.8, 8.2 Hz), 4.95 (m,
1H), 4.30 (m, 1H), 4.24 (m, 2H), 4.10 (m, 2H), 3.25
(broad, 1H), 2.90-0.80 (m, 15H).

Example 30

trans-N2-(4-(2-Thienylsulfonyl)aminomethyl)-cyclohexyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]-

5 cyclohepta[d][1,3]thiazol-2-amine: ¹H NMR (CDCl₃) δ 1.15 (4H, m), 1.45 (1H, m), 1.80 (2H, m), 2.07 (2H, m), 2.20 (2H, m), 2.82 (6H, m), 3.25 (1H, m), 5.00 (2H, m), 6.82 (1H, m), 7.05 (1H, m), 7.10 (1H, t, *J* = 4.4 Hz), 7.62 (3H, m).

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Example 31

trans-N2-(4-Ethylsulfonylaminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-

15 amine: ¹H NMR (CDCl₃) δ 1.15 (4H, m), 1.38 (3H, t, *J* = 7.4 Hz), 1.45 (1H, m), 1.90 (2H, m), 2.10 (2H, m), 2.25 (2H, m), 2.80 (2H, m), 2.86 (2H, t, *J* = 6.9 Hz), 2.97 (2H, t, *J* = 6.6 Hz), 3.05 (2H, q, *J* = 7.4 Hz), 3.30 (1H, broad), 4.50 (1H, m), 4.97 (1H, m), 6.83 (1H, m), 7.07 (1H, m),
20 7.66 (1H, m).

Example 32

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(1-methylimidazolyl-4-yl)sulfonylaminomethyl}cyclohexyl-amino-3-thia-

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benzo[e]azulene in 33% yield: ¹H NMR (CDCl₃) δ 7.67 (dd, 1H, *J*=10.8, 3.0 Hz), 7.52 (s, 1H), 7.48 (s, 1H), 7.05 (dd, 1H, *J*=6.0, 8.2 Hz), 6.82 (apparent dt, 1H, *J*=2.8, 8.3 Hz), 5.43 (broad, 1H), 5.01 (d, 1H, *J*=8.0 Hz), 3.76 (s, 3H),
30 3.22 (m, 1H), 2.90-2.70 (m, 5H), 2.30-0.80 (m, 9H).

Example 33

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trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(3,5-dimethylisoxazol-4-yl)sulfonylaminomethyl}cyclohexyl-amino-3-thia-benzo[e]azulene in 87% yield: ^1H NMR (CDCl_3) δ 7.55 (dd, 1H, $J=10.8, 3.0$ Hz), 7.05 (dd, 1H, $J=6.0, 8.2$ Hz), 6.81 (apparent dt, 1H, $J=2.8, 1.3$ Hz), 5.95 (broad, 1H), 5.30 (broad, 1H), 3.20-2.70 (m, 5H), 2.61 (s, 3H), 2.38 (s, 3H), 2.20-0.80 (m, 9H).

Example 34

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-methylsulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene was obtained as a white solid in 41% yield: m.p. 179-181 °C; ^1H NMR δ 7.67 (dd, 1H, $J = 2.8, 10.8$ Hz), 7.07 (dd, 1H, $J = 6.0, 8.2$ Hz), 6.84 (td, 1H, $J = 2.8, 8.2$ Hz), 4.96 (b, 1H), 4.52 (b, 1H), 3.32 (b, 2H), 3.00 (s, 3H), 2.86 (t, 2H, $J = 6.9$ Hz), 2.79 (m, 2H), 2.26 (m, 2H), 2.17 (m, 4H), 1.35 (m, 4H); 410 (ESMS, MH^+).

Example 35

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-diethylamino-sulfonylamino)cyclohexylamino-3-thia-benzo[e]azulene was obtained as a tan solid in 13% yield: m.p. 172-174 °C; ^1H NMR δ 7.68 (dd, 1H, $J = 2.8, 10.8$ Hz), 7.06 (dd, 1H, $J = 5.8, 8.3$ Hz), 6.84 (td, 1H, $J = 2.7, 8.2$ Hz), 4.82 (m, 1H), 3.96 (d, 1H, $J = 7.5$ Hz), 3.38 (m, 1H), 3.27 (q, 4H, $J = 7.1$ Hz), 3.17 (m, 1H), 2.86 (t, 2H, $J = 6.9$ Hz), 2.80 (m, 2H), 2.27-2.03 (m, 6H), 1.32 (m, 2H), 1.20 (t, 6H, $J = 7.1$ Hz); 467 (ESMS, MH^+).

Example 36

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trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(4-methoxy-phenyl)sulfonylamino)cyclohexylamino-3-thia-benzo[e]-azulene was obtained as a yellow syrup in 50% yield: ^1H NMR δ 7.82 (d, 2H, J = 8.9 Hz), 7.65 (dd, 1H, J = 2.8, 10.8 Hz), 7.05 (dd, 1H, J = 6.0, 8.2 Hz), 6.98 (d, 2H, J = 8.9 Hz), 6.82 (td, 1H, J = 2.9, 8.3 Hz), 4.83 (d, 1H, J = 7.7 Hz), 4.55 (d, 1H, J = 7.5 Hz), 3.88 (s, 3H), 3.27 (m, 1H), 3.10 (m, 1H), 2.84 (t, 2H, J = 6.9 Hz), 2.78 (m, 2H), 2.16-2.02 (m, 4H), 1.89 (m, 2H), 1.24 (m, 4H); 502 (ESMS, MH^+).

Example 37

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-thienyl)-sulfonyl-amino)cyclohexylamino-3-thia-benzo[e]azulene was obtained as a tan solid in 36% yield: m.p. 230-231 °C; ^1H NMR δ 7.67-7.58 (m, 3H), 7.10-7.03 (m, 2H), 6.81 (td, 1H, J = 2.8, 8.3 Hz), 4.87 (m, 1H), 4.79 (m, 1H), 3.26 (m, 2H), 2.84 (t, 2H, J = 6.9 Hz), 2.77 (m, 2H), 2.18-2.02 (m, 4H), 1.93 (m, 2H), 1.28 (m, 4H); 478 (ESMS, MH^+).

Example 38

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoro-ethyl)sulfonylamino)cyclohexylamino-3-thia-benzo[e]azulene was obtained as a yellow solid in 32% yield: m.p. 89-91 °C; ^1H NMR δ 7.68 (dd, 1H, J = 2.7, 10.8 Hz), 7.07 (dd, 1H, J = 6.0, 8.2 Hz), 6.84 (td, 1H, J = 2.8, 8.3 Hz); 4.78 (m, 1H), 4.72 (m, 1H), 3.82 (q, 2H, J = 8.9 Hz), 3.38 (m, 2H), 2.89-2.81 (m, 4H), 2.28 (m, 2H), 2.10 (m, 4H), 1.47-1.30 (m, 4H); 478 (ESMS, MH^+).

Example 39

1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoroethyl)-sulfonylamino)butylamino-3-thia-benzo[e]azulene (TFA salt)
5 was obtained as a white solid in 35% yield: m.p. 140-141 °C; 452 (ESMS, MH⁺).

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Example 40

trans-1-Aza-9-fluoro-2-{4-(3,4-difluorophenyl)-sulfonyl-aminomethyl}cyclohexylamino-4,5-dihydro-3-thia-
15 benzo[e]azulene: 522 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.74-7.63 (m, 2H), 7.60 (dd, 1H, J=2.7, 10.8 Hz), 7.32 (apparent dq, 1H, J=7.6, 1.0), 7.06 (dd, 1H, J=6.0, 8.3 Hz), 6.82 (apparent dt, 1H, J=2.8, 8.2 Hz), 5.05-4.95 (m, 2H), 3.25 (m, 1H), 2.95-2.60 (m, 6H), 2.05 (m, 2H), 2.01
20 (ABm, 4H), 1.62 (broad, 1H), 1.41 (m, 1H), 1.30-0.80 (m, 4H).

Example 41

25 trans-1-Aza-9-fluoro-2-{4-trifluoromethylsulfonyl-aminomethyl}cyclohexylamino-4,5-dihydro-3-thiabenz[e]azulene in 17% yield: 446 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.69 (dd, 1H, J=2.7, 10.8 Hz), 7.05 (dd, 1H, J=6.0, 8.3 Hz), 6.82 (apparent dt, 1H, J=2.8, 8.2 Hz), 4.87 (d, 1H, J=8.0 Hz), 4.61 (m, 1H), 3.29 (m, 1H), 3.00 (t, 2H, J=9.2 Hz), 2.86 (t, 2H, J=6.9 Hz), 2.83-2.77 (m, 2H), 2.06 (m, 2H), 2.01 (ABm, 4H), 1.80-1.00 (m, 6H).

Example 42

trans-1-Aza-9-fluoro-2-{4-(2-fluoro)phenylsulfonyl-amino}-
cyclohexylmethylamino-4,5-dihydro-3-thia-benzo[e]azulene
in 100% yield: 504 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 7.90
5 (apparent dt, 1H, $J=1.1$ average, 7.7 Hz), 7.63 (dd, 1H,
 $J=2.8$, 10.7 Hz), 7.57 (apparent dq, 1H, $J=1.1$, 3.5 Hz),
7.56-7.17 (m, 2H), 7.04 (dd, 1H, $J=6.0$, 8.3 Hz), 6.82
(apparent dt, 1H, $J=2.8$, 8.3 Hz), 5.46 (broad, 1H), 4.94
(d, 1H, $J=5.7$ Hz), 3.15 (m, 1H), 3.05 (m, 2H), 2.83 (t,
10 2H, $J=6.9$ Hz), 2.05-0.75 (m, 12H).

Example 43

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-9-fluoro-
15 5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-
amine: A mixture of trans-N2-(4-amino)cyclohexylmethyl-9-
fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-
2-amine dihydrochloride (418 mg, 1.0 mmol) and
triethylamine (1.25 mL) in THF (6 mL) was cooled in an ice
20 water bath and treated with methanesulfonyl chloride
dropwise (0.10 mL). The mixture was stirred at room
temperature for 30 minutes and then poured into water (60
mL). The product was extracted into chloroform and
purified by flash chromatography over silica gel
25 (EtOAc/hexane 1:1) to afford a yellow solid (227 mg, 54%
yield): CIMS m/e = 424 (MH^+); 1H NMR (300 MHz, $CDCl_3$) δ
1.0-1.3 (4H, m), 1.4-1.6 (1H, m), 1.84 (2H, d, J = 12.3
Hz), 2.0-2.2 (4H, m), 2.77 (2H, t, J = 5.4 Hz), 2.84 (2H,
t, J = 6.9 Hz), 2.97 (3H, s), 3.07 (2H, t, J = 6.1 Hz),
30 3.1-3.30 (1H, m), 4.66 (1H, d, J = 7.6 Hz), 5.52 (1H, t, J
= 4.5 Hz), 6.83 (1H, dt, J = 2.8, 8.2 Hz), 7.06 (1H, dd, J
= 5.9, 8.2 Hz), 7.65 (1H, dd, J = 2.7, 10.7 Hz).

Example 44

trans-N²-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine

a. *trans*-1-Aminomethyl-4-(benzyloxycarbonylamino)-cyclohexane: To a solution of *trans*-1-(*t*-butyloxycarbonylaminomethyl)-4-(benzyloxycarbonyl-amino)-cyclohexane (20 g, 55.2 mmol) in EtOAc (790 mL) was added 4N HCl in dioxane (200 mL). The mixture was stirred overnight and then concentrated to give a white solid: ¹H NMR (300 MHz, CD₃OD) δ 1.0-1.3 (4H, m), 1.50-1.67 (1H, m), 1.83 (2H, d, *J* = 12.3 Hz), 1.96 (2H, d, *J* = 10.3 Hz), 2.77 (2H, d, *J* = 7.0 Hz), 3.20-3.40 (1H, m), 5.03 (1H, s), 7.20-7.40 (5H, m).

b. *trans*-1-Aminocarbothioylaminomethyl-4-(benzyloxycarbonylamino)cyclohexane: *trans*-1-Aminomethyl-4-(benzyloxycarbonylamino)cyclohexane (55.2 mmol) was dissolved in a mixture of chloroform (350 ml) and triethylamine (16 mL), cooled in an ice water bath and treated with benzoylisothiocyanate (10 ml, 74.4 mmol). The mixture was stirred for 6 hours before it was allowed to slowly warm to room temperature overnight. The solvent was evaporated and the residue triturated with MeOH (800 ml) and potassium carbonate (70 g) solution in water (800 ml). The mixture was heated at reflux for 10 min. and then additional aqueous potassium carbonate solution (34 g/140 ml) was added. The mixture was cooled to 8 °C. The resulting precipitate was collected by filtration and washed with water and ether (200 mL) to give the desired product as a white solid (12.02 g, 68%): m.p. 155-158 °C; ¹H NMR (300 MHz, CD₃OD) δ 0.9-1.3 (4H, m), 1.4-1.55 (1H,

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m), 1.79 (2H, d, $J = 9.5$ Hz), 1.92 (2H, d, $J = 10.0$ Hz), 2.95 (1H, d, $J = 6.0$ Hz), 3.20-3.40 (2H, m), 5.03 (2H, s), 7.20-7.40 (5H, m).

5 c. *trans*-N2-(4-Benzyloxycarbonylamino)cyclohexyl-methyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]-
cyclohepta[d][1,3]thiazol-2-amine: A mixture of *trans*-1-aminocarbothioylaminomethyl-4-(benzyloxy-
carbonylamino)cyclohexane (4.46 g, 13.9 mmol), 2-bromo-8-
10 fluoro-1-benzosuberone (4.08 g, 15.9 mmol), and *N,N*-diisopropylethylamine (4.6 mL) in ethanol (95 ml) was
heated at reflux for 6 hours. The solvent was evaporated
and the residue washed with water (200 ml). Ether (10 ml)
was then added and the suspension filtered. The solid was
15 washed with ether (10 ml) to give a white solid (5.55 g,
83%): CIMS $m/e = 480$ (MH^+); 1H NMR (300 MHz, $CDCl_3$) δ 1.0-
1.2 (4H, m), 1.40-1.55 (1H, m), 1.89 (2H, d, $J = 7.7$ Hz),
2.00-2.16 (4H, m), 2.77 (2H, t, $J = 5.4$ Hz), 2.86 (2H, t,
 $J = 6.9$ Hz), 3.13 (2H, t, $J = 6.4$ Hz), 3.4-3.6 (1H, m),
20 4.30 (1H, d, $J = 6$ Hz), 5.05 (1H, m), 5.09 (2H, s), 6.8
(1H, dt, $J = 2.8, 8.4$ Hz), 7.06 (1H, dd, $J = 5.7, 8.4$ Hz),
7.35 (5H, m), 7.69 (1H, dd, $J = 2.8, 10.8$ Hz).

d. *trans*-N2-(4-Amino)cyclohexylmethyl-9-fluoro-5,6-
25 dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine:
trans-N2-(4-Benzyloxycarbonylamino)cyclohexyl-methyl-9-
fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-amine (5.55 g) was heated at reflux in a
mixture of trifluoroacetic acid (50 ml) and water (5 ml)
30 for 30 min. Most of the solvent was evaporated and the
residue poured into water (150 ml). Potassium carbonate
was added until the pH reached 10. The product was
extracted into chloroform and converted to the
hydrochloride salt which was isolated as an off-white

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solid: ^1H NMR of the free base (300 MHz, CDCl_3) δ 1.1-1.6 (4H, m), 1.3-1.7 (4H, m), 1.80-2.00 (4H, m), 2.00-2.20 (2H, m), 2.30 (1H, m), 2.79 (2H, t, $J = 5.5$ Hz), 2.86 (2H, 5, $J = 6.9$ Hz), 3.12 (2H, t, $J = 6.2$ Hz), 5.07 (1H, t),
5 6.82 (1H, dt, $J = 2.8$ Hz), 7.05 (1H, dd, $J = 5.9, 8.3$ Hz), 7.70 (1H, dd, $J = 2.8, 10.8$ Hz).

e. *trans*-N2-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-
10 thiazol-2-amine: A mixture of *trans*-N2-(4-amino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4*H*-benzo-[6,7]cyclohepta[d][1,3]-thiazol-2-amine dihydrochloride (524 mg, 1.25 mmol), sulfamide (371 mg) and triethylamine (1 mL) in THF (7 mL), methanol (5 mL) and water (7 mL) was
15 heated at reflux for 18 hours. Most of the solvent was evaporated and then water (50 mL) was added. The product was extracted into chloroform and then purified by flash chromatography over silica gel (EtOAc/hexane 5:4) to give the desired product as a yellow solid (238 mg, 56%): m.p.
20 180-182 °C; CIMS $m/e = 425$ (MH^+); ^1H NMR (300 MHz, CDCl_3) δ 1.00-1.30 (4H, m), 1.40-1.60 (1H, m), 1.81 (2H, d, $J = 12.0$ Hz), 2.00-2.20 (4H, m), 2.75 (2H, t, $J = 5.3$ Hz), 2.82 (2H, t, $J = 6.9$ Hz), 3.02 (2H, d, $J = 6.4$ Hz), 3.20 (1H, m), 4.85 (1H, d, $J = 6.7$ Hz), 5.20 (2H, s), 5.85 (1H, s),
25 6.83 (1H, dt, $J = 2.8, 8.2$ Hz), 7.05 (1H, dd, $J = 5.9, 8.3$ Hz), 7.58 (1H, dd, $J = 2.8, 10.7$ Hz).

Example 45

30 9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine: 6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-5-one (1.0 g, 3.89 mmole) was mixed with thiourea (355 mg, 4.66 mmole) in 20 mL of ethanol and heated at reflux temperature for 16 hours. The reaction

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mixture was cooled and filtered to give a solid (m.p. 270 °C). The filtrate was concentrated and then partitioned between ethyl acetate and saturated sodium carbonate solution. The organic extract was concentrated and chromatographed (silica, ethyl acetate/hexanes) to give the desired product as a yellow solid (m.p. 142-144 °C, 34%).

N1-(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-yl)-5-bromopentanamide:

9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine (150 mg, 0.640 mmole) was dissolved in 3 ml of dry THF, mixed with triethylamine (135 µl, 0.970 mmole), cooled in an ice bath and treated with 5-bromovaleryl chloride (90 µl, 0.67 mmole). The mixture was stirred at room temperature for 3 days. TLC analysis of the mixture showed 50% completion. Hence, a catalytic amount of DMAP was added and stirring was continued for 16 hours. There was no change in the TLC of the mixture. 5-Bromovaleryl chloride (90 µl) was added and stirred for 3 days. The reaction mixture was partitioned between ethyl acetate and saturated sodium carbonate and the aqueous phase separated and extracted with 2X3 ml ethyl acetate. The combined ethyl acetate extracts were washed with saturated sodium chloride solution, concentrated and chromatographed (silica, Ethyl acetate/hexanes) to give 179 mg of the desired product as a white foam (70%): 397, 399 (ESMS, MH+).

1-5-[(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
[d][1,3]-thiazol-2-yl)amino]-5-oxopentyl-1,2-triazadien-2-
ium:

N1-(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-yl)-5-bromopentanamide (179 mg, 0.45

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mmole) was dissolved in 1.5 ml of dry DMSO and treated with 72 mg of ammonium chloride (1.35 mmole) and 59 mg of sodium azide (0.91 mmole). After 5 hours, the mixture was heated at 60 °C for 16 hours. The reaction mixture was cooled, quenched with ice-water, extracted with ethyl acetate (3x3 ml), and the combined ethyl acetate extracts washed with water, and concentrated to give 145 mg of a yellow solid (90%): 360 (ESMS, MH⁺).

10 N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl)-5-aminopentanamide:
3907-50-2 1-5-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-yl)amino]-5-oxopentyl-1,2-triazadien-2-ium (145 mg, 0.40 mmole) was dissolved in 2
15 ml of THF and treated with P(CH₃)₃ in THF (1M, 0.80 ml, 0.8 mmol) and water (22 µL, 1.22 mmole). The resulting mixture was stirred at room temperature for 16 hours and the solvent evaporated. The residue was dissolved in ethyl acetate and chromatographed over silica gel (14 g)
20 eluting with ethyl acetate and then with EtOAc/7M NH₃ in MeOH (20:3) to give an oil (115 mg).

N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl)-5-[(methylsulfonyl)amino]-
25 pentanamide:
N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl)-5-aminopentanamide (115 mg, 0.34 mmole) was dissolved in 2 ml of dry THF, cooled with an ice bath, triethylamine was added (96 µl, 0.69 mmole)
30 followed by addition of 27 µl of methane sulfonyl chloride (0.35 mmole). The reaction mixture was stirred at room temperature for 6 hours, quenched with saturated sodium carbonate solution and extracted with 3x3 ml of ethyl acetate. The combined ethyl acetate extracts were washed

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with saturated sodium chloride solution, concentrated and chromatographed (12 g of silica gel, EtOAc/hexanes/7N NH₃ in MeOH, 50:50:2) to give 53 mg of the desired product as a white solid (38%): m.p. 145-147 °C;
5 412 (ESMS, MH⁺).

Example 46

10 *trans*-N2-(4-Aminosulfonylaminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine

a. 2,3,4,5-Tetrahydro-1-benzoxepin-5-one To a solution of P₂O₅ (62 g) in methanesulfonic acid (415 ml) was added a solution of 4-phenoxybutyric acid (16 g) in
15 methanesulfonic acid (120 ml) in 4 portions every 2 hours. After the last addition, the mixture was allowed to stand for another 2 hours before it was poured onto ice (3 Kg). The mixture was neutralized with 50% NaOH solution and the product extracted into chloroform. Purification by flash
20 chromatography over silica gel (EtOAc/hexane 1:10) afforded an oil (5.06 g, 35%): ¹H NMR (300 MHz, CDCl₃) δ 2.22 (2H, m), 2.91 (2H, t, J = 7.0 Hz), 4.25 (2H, t, J = 6.6 Hz), 7.10 (2H, m), 7.43 (1H, dt, J = 1.8, 7.5 Hz), 7.77 (1H, dd, J = 1.6, 7.7 Hz).

25 b. 4-Bromo-2,3,4,5-tetrahydro-1-benzoxepin-5-one: To a solution of 2,3,4,5-tetrahydro-1-benzoxepin-5-one (5.06 g, 31.2 mmol) in acetic acid (50 ml) cooled by an ice water bath was added bromine (1.75 ml) dropwise. The solvent
30 was evaporated to give the product as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 2.40-2.60 (1H, m), 2.90-3.00 (1H, m), 4.08-4.18 (1H, m), 4.42-4.49 (1H, m), 4.99 (1H, dd, J = 8.1, 7.0 Hz), 7.07 (1H, d, J = 8.3 Hz), 7.12 (1H, t, J =

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7.5 Hz), 7.45 (1H, dt, $J = 1.6, 7.7$ Hz), 7.75 (1H, dd, $J = 1.7, 7.8$ Hz).

c *trans*-N2-(4-(*t*-Butyloxycarbonylaminomethyl)-cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-*d*][1,3]thiazol-2-amine:
A mixture of 4-bromo-2,3,4,5-tetrahydro-1-benzoxepin-5-one (7.6 mmol), *trans*-1-(aminocarbothioylamino)-4-(*t*-butyloxycarbonylaminomethyl)cyclohexane (6.9 mmol) and *N,N*-diisopropylethylamine (2.5 mL) in ethanol (48 mL) was heated at reflux for 6 hours. The solvent was evaporated and the residue flash chromatographed over silica gel (EtOAc/hexane 1:3) to give a yellow solid (1.97 g, 66%): ^1H NMR (300 MHz, CDCl_3) δ 1.00-1.15 (4H, m), 1.44 (10H, s), 1.82 (2H, d, $J = 11.8$ Hz), 2.21 (2H, d, $J = 11.9$ Hz), 2.99 (2H, t, $J = 6.4$ Hz), 3.14 (2H, t, $J = 5.1$ Hz), 3.2-3.25 (1H, m), 4.32 (2H, t, $J = 5.2$ Hz), 4.64 (1H, t, $J = 4.7$ Hz), 4.94 (1H, d, $J = 8.0$ Hz), 6.98 (1H, dd, $J = 1.3, 7.8$ Hz), 7.07 (1H, dt, $J = 1.4, 7.5$ Hz), 7.14 (1H, dt, $J = 1.8, 7.5$ Hz), 8.24 (1H, dd, $J = 1.8, 7.8$ Hz).

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d. *trans*-N2-(4-Aminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-*d*][1,3]thiazol-2-amine dihydrochloride: *trans*-N2-(4-(*t*-butyloxy-carbonylaminomethyl)cyclohexyl-4,5-dihydro-benzo-[2,3]oxepino[4,5-*d*][1,3]thiazol-2-amine (1.97 g, 4.58 mmol) in EtOAc (50 mL) and 4M HCl in dioxane (12 mL) was stirred at room temperature overnight. The solvent was evaporated to give a yellow solid (1.85 g, 99%): m.p. 245 °C (dec.); ^1H NMR (300 MHz, CD_3OD) δ 1.20-1.30 (2H, m), 1.45-1.60 (2H, m), 1.70 (1H, m), 1.95 (2H, d, $J = 9.8$ Hz), 2.21 (2H, d, $J = 10.8$ Hz), 2.83 (2H, d, $J = 6.9$ Hz), 3.17 (2H, t, $J = 5.4$ Hz), 3.50-3.70 (1H, m), 4.33 (2H, t, $J = 5.5$ Hz), 7.11 (1H, d, $J = 8.1$ Hz), 7.21 (1H, t, $J = 7.5$ Hz), 7.36 (1H, t, $J = 8.1$ Hz), 7.70 (1H, d, $J = 7.8$ Hz).

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e. *trans*-N2-(4-Aminosulfonylaminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: A mixture of *trans*-N2-(4-aminomethyl)-cyclohexyl-4,5-dihydro-benzo[2,3]oxepino-[4,5-d][1,3]thiazol-2-amine dihydrochloride (402 mg, 1 mmol), sulfamide (288 mg, 3 mmol) and triethylamine (0.56 ml) in ethanol (2.5 ml) and water (2.5 ml) was heated at reflux for 3 hours before it was poured into water (50 ml). The product was extracted into chloroform and then purified by flash chromatography over silica gel (EtOAc/hexane 2:1) to afford the desired product as a white solid (362 mg, 89%): m.p. 170-173 °C; CIMS m/e = 409 (MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 1.0-1.3 (4H, m), 1.5-1.7 (1H, m), 1.89 (2H, d, *J* = 12.3 Hz), 2.26 (2H, d, *J* = 11.5 Hz), 3.01 (2H, t, *J* = 6.5 Hz), 3.15 (2H, t, *J* = 5.2 Hz), 3.20-3.40 (1H, m), 4.33 (2H, t, *J* = 5.1 Hz), 4.43 (1H, t, *J* = 6.1 Hz), 4.59 (1H, s, broad), 4.92 (1H, s, broad), 6.99 (1H, d, *J* = 7.9 Hz), 7.08 (1H, t, *J* = 7.4 Hz), 7.16 (1H, dt, *J* = 1.7, 7.2 Hz), 8.23 (1H, dd, *J* = 1.7, 7.8 Hz).

Example 47

trans-N2-(4-Methylsulfonylaminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: A mixture of *trans*-N2-(4-aminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine dihydrochloride (345 mg, 0.87 mmol) and triethylamine (1.1 ml) in THF (5 ml) was cooled in an ice water bath and treated with methanesulfonyl chloride (0.087 ml). After stirring for 30 minutes at room temperature, the mixture was poured into water (50 ml) containing potassium carbonate (1 g). The product was extracted into chloroform and purified by flash chromatography

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(EtOAc/hexane 2:1) to give a yellow solid (308 mg, 88% yield): m.p. 67-69 °C; CIMS m/e = 408 (MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 0.90-1.40 (5H, m), 1.76 (2H, d, J = 11.7 Hz), 2.15 (2H, d, J = 10.5 Hz), 2.80-3.00 (5H, m), 3.14 (3H, m), 4.30 (2H, t, J = 4.7 Hz), 5.25 (1H, t, J = 4.7 Hz), 5.35 (1H, d, J = 7.9 Hz), 6.98 (1H, d, J = 7.8 Hz), 7.06 (1H, t, J = 7.5 Hz), 7.14 (1H, t, J = 7.4 Hz), 8.19 (1H, d, J = 7.6 Hz).

Example 48

trans-1-Aza-4,5-dihydro-2-{4-(2-methoxy-5-methyl)phenyl-sulfonylaminomethyl}cyclohexylamino-6-oxa-3-thia-benzo[e]azulene: 91% yield; 514 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.20 (dd, 1H, J=1.6, 7.8 Hz), 7.68 (d, 1H, J=2.1 Hz), 7.30 (dd, 1H, J=2.1, 8.4 Hz), 7.10 (apparent dt, 1H, J=1.1, 7.4 Hz), 7.01 (apparent dt, 1H, J=1.1, 7.5 Hz), 6.96 (d, 1H, J=7.1 Hz), 6.90 (d, 1H, J=8.5 Hz), 5.27 (t, 2H, J=3.8 Hz), 4.29 (t, 2H, 5.2 Hz), 3.90 (s, 3H), 3.18 (m, 1H), 3.11 (t, 2H, J= 5.1 Hz), 2.66 (t, 2H, J=6.5 Hz), 2.31 (s, 3H), 1.95 (ABm, 4H), 1.40-0.80 (m, 8H); m.p. (HCl salt) 100-105 °C (decomp.)

Example 49

N1-(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]-thiazol-2-yl)-5-[(2-methoxy-5-methylphenyl)-sulfonyl]-aminopentanamide
N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d]-[1,3]-thiazol-2-yl)-5-aminopentanamide (42 mg, 0.13 mmole) was dissolved in 2 ml of dry THF, cooled in an ice bath, triethylamine was added (36 µl, 0.26 mmole) followed by addition of 9 mg of o-methoxy-m-toluenesulfonyl chloride (0.13 mmole). The reaction mixture was stirred at room

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temperature for 6 hours, quenched with saturated sodium carbonate solution and extracted with 3x3 ml of ethyl acetate. The combined ethyl acetate extracts were washed with saturated sodium chloride solution, concentrated and chromatographed (13 g of silica gel, EtOAc/hexanes/7N NH₃ in MeOH, 50:50:2) to give the desired product: m.p. 70-75 °C; 518 (ESMS, MH⁺)

Example 50

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine as a yellow solid: m.p. 64-67 °C; 408 (ESMS, MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 1.0-1.4 (4H, m), 1.92 (2H, d, J = 12.7 Hz), 2.12 (2H, d, J = 11.7 Hz), 2.98 (3H, s), 3.16 (4H, m), 3.25 (1H, m), 4.12 (1H, d, J = 7.5 Hz), 4.33 (2H, t, J = 5.0 Hz), 5.1 (1H, broad), 7.07 (1H, d, J = 7.2 Hz), 7.11 (1H, t, J = 7.9 Hz), 7.16 (1H, t, J = 7.0 Hz), 8.24 (1H, d, J = 7.5 Hz).

Example 51

trans-1-Aza-4,5-dihydro-2-{4-(2-methoxy-5-methyl-phenyl)-sulfonylamino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene in 41% yield: m.p. 220-224 °C; 514 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.22 (dd, 1H, J=1.6, 7.8 Hz), 7.71 (d, 1H, J=2.1 Hz), 7.32 (dd, 1H, J=2.1, 8.4 Hz), 7.18 (apparent dt, 1H, J=1.1, 7.4 Hz), 7.05 (apparent dt, 1H, J=1.1, 7.5 Hz), 6.97 (d, 1H, J=7.1 Hz), 6.91 (d, 1H, J=8.5 Hz), 5.13 (t, 1H, J=6.0 Hz), 4.83 (d, 1H, J=7.2 Hz), 4.31 (t, 2H, J=5.2 Hz), 3.93 (s, 3H), 3.13 (t, 2H, J=5.2 Hz), 3.05 (t, 2H, J=6.3 Hz), 3.02 (m, 1H), 2.34 (s, 3H), 1.90-0.80 (m, 12H).

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Example 52

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-9-fluoro-
5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-
5 amine as a white solid: m.p. 140-142 °C; CIMS m/e = 424
(MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 1.00-1.40 (4H, m), 1.37
(3H, t, J = 7.4 Hz), 1.91 (2H, d, J = 12.5 Hz), 2.00-2.20
(4H, m), 2.79 (2H, t, J = 5.5 Hz), 2.86 (2H, t, J = 6.9
Hz), 3.04 (2H, q, J = 7.4 Hz), 3.13 (2H, t, J = 6.3 Hz),
10 3.10-3.30 (1H, m), 4.04 (1H, d, J = 7.8 Hz), 5.09 (1H,
broad), 6.84 (1H, dt, J = 2.8, 8.2 Hz), 7.06 (1H, dd, J =
5.9, 8.3 Hz), 7.68 (1H, dd, J = 2.8, 10.8 Hz).

Example 53

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trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-isopropyl-
sulfonylamino}cyclohexylmethylamino-3-thia-benzo[e]-
azulene in 15% yield: 452 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ
7.76 (dd, 1H, J=2.7, 10.6 Hz), 7.05 (dd, 1H, J=6.0, 8.2
20 Hz); 6.82 (apparent dt, 1H, J=2.8, 8.3 Hz), 5.69 (m, 1H),
4.56 (d, 1H, J=8.4 Hz), 3.20-2.90 (m, 4H); 2.83 (t, 2H,
J=7.0 Hz), 2.78 (m, 2H), 2.20-0.80 (m, 12H), 1.48 (d, 6H,
J=7.0 Hz).

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Example 54

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl-
sulfonylamino)cyclohexyl)amino-3-thia-benzo[e]azulene
(hydrogen chloride salt) was obtained as a white solid in
30 65% yield: m.p. (HCl salt) 165-167 °C; ¹H NMR (CD₃OD) δ
9.27 (s, 1H), 9.02 (m, 1H), 8.86 (d, 1H, J = 8.0 Hz), 8.15
(m, 1H), 7.34 (m, 2H), 7.09 (td, 1H, J = 2.3, 8.6 Hz),
3.58 (b, 1H), 3.27 (b, 1H), 2.76 (m, 4H), 2.21-2.07 (m,
4H), 1.92 (m, 2H), 1.47 (m, 4H); 473 (ESMS, MH⁺).

Example 55

1-Aza-9-fluoro-4,5-dihydro-2-(5-(3-pyridyl)sulfonyl-
5 amino)pentylamino-3-thia-benzo[e]azulene (hydrogen
chloride salt) was obtained as a white solid in 66% yield:
m.p. (HCl salt) 84-86 °C; ¹H NMR (free base, CD₃OD) δ 9.25
(broad, 1H), 9.05 (b, 1H), 8.85 (d, 1H, J = 8.1 Hz), 8.18
(m, 1H), 7.36 (m, 2H), 7.09 (td, 1H, J = 2.4, 8.4 Hz),
10 3.47 (t, 2H, J = 6.9 Hz), 3.02 (t, 2H, J = 6.6 Hz), 2.78
(m, 4H), 2.17 (m, 2H), 1.75 (m, 2H), 1.64-1.48 (m, 4H);
461 (ESMS, MH⁺).

Example 56

15 1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl)sulfonyl-
amino)butylamino-3-thia-benzo[e]azulene (hydrogen chloride
salt) was obtained as a light yellow solid in 56% yield:
m.p. (HCl salt) 101-103 °C; ¹H NMR (free base, CD₃OD) δ
20 9.13 (m, 1H), 8.91 (m, 1H), 8.59 (m, 1H), 7.94 (m, 1H),
7.36 (m, 2H), 7.10 (td, 1H, J = 2.7, 8.4 Hz), 3.48 (t, 2H,
J = 6.9 Hz), 3.02 (t, 2H, J = 6.5 Hz), 2.78 (m, 4H), 2.19
(m, 2H), 1.80 (m, 2H), 1.65 (m, 2H); 447 (ESMS, MH⁺).

Example 57

25 1-Aza-9-fluoro-4,5-dihydro-2-{2-(2-methylsulfonyl-
amino)ethoxy}ethylamino-3-thia-benzo[e]azulene in 76%
yield: m.p. 159-162 °C; ¹H NMR (CDCl₃) δ 7.75 (dd, 1H,
30 J=2.5, 10.7 Hz), 7.06 (dd, 1H, J=6.0, 8.1 Hz), 6.83
(apparent dt, 1H, J=2.8, 8.3 Hz), 5.42 (broad, 1H), 5.14
(b, 1H), 3.69 (t, 2H, J=4.9 Hz), 3.61 (t, 2H, J=4.8 Hz),
3.51 (broad q, 2H, J=4.3 Hz), 3.31 (q, 2H, J=4.8 Hz), 2.98
(s, 3H), 2.86 (t, 2H, J=6.9 Hz), 2.07 (m, 2H).

Example 58

1-Aza-9-fluoro-4,5-dihydro-2-{2-[2-(2-methoxy-5-methylphenyl)sulfonylamino]ethoxy}ethylamino-3-thia-
benzo[e]azulene in 87% yield: 506 (ESMS, MH^+); 1H NMR
($CDCl_3$) δ 7.73-7.68 (m, 2H), 7.34 (dd, 1H, $J=2.1, 10.1$ Hz),
6.94 (d, 1H, $J=8.4$ Hz), 6.84 (apparent dt, 1H, $J=2.8, 8.2$
Hz), 5.43 (t, 1H, $J=6.0$ Hz), 5.23 (m, 1H), 3.94 (s, 3H),
3.51-3.43 (m, 4H), 3.09 (q, 2H, $J=5.5$ Hz), 2.87 (t, 2H,
 $J=6.9$ Hz), 2.82-2.78 (m, 2H), 2.12-2.00 (m, 2H); m.p. (HCl
salt) 56-60 °C.

Example 59

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl)-sulfonylaminomethyl)cyclohexylamino-3-thia-benzo[e]-
azulene (hydrogen chloride salt) was obtained as a light
yellow solid in 69% yield: m.p. (HCl salt) 127-129 °C; 1H
NMR (free base, CD_3OD) δ 9.08 (d, 1H, $J = 1.9$ Hz), 8.81 (d,
1H, $J = 4.8$ Hz), 8.15 (m, 1H), 7.47 (m, 2H), 7.05 (dd, 1H,
 $J = 6.0, 8.2$ Hz), 6.80 (td, 1H, $J = 2.7, 8.2$ Hz), 5.98 (m,
1H), 5.33 (m, 1H), 3.14 (m, 1H), 2.83 (t, 2H, $J = 6.9$ Hz),
2.76 (m, 4H), 2.10 (m, 4H), 1.73 (m, 2H), 1.23 (m, 1H),
1.10 (m, 2H), 0.95 (m, 2H); 487 (ESMS, MH^+).

Example 60

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-8-methoxy-
4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine
as a yellow solid: m.p. 170-172 °C; 452 (ESMS, MH^+); 1H NMR
 δ 1.20 (4H, m), 1.37 (3H, t, $J = 7.4$ Hz), 1.90 (2H, m),
2.10 (2H, m), 3.04 (2H, q, $J = 7.4$ Hz), 3.13 (4H, m), 3.25
(1H, broad), 3.80 (3H, s), 3.96 (1H, d, $J = 7.7$ Hz), 4.33

(2H, t, $J = 5.1$ Hz), 5.02¹²⁶ (1H, broad), 6.55 (1H, d, $J = 2.5$ Hz), 6.66 (1H, dd, $J = 2.6, 8.6$ Hz), 8.15 (1H, d, $J = 8.8$ Hz).

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Example 61

trans-1-Aza-4,5-dihydro-8-methoxy-2-{4-methyl-sulfonyl-amino)cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene in 59% yield: m.p. 65-70 °C; 438 (ESMS, MH^+); 1H NMR (CDCl₃) δ 8.15 (d, 1H, $J=8.9$ Hz), 6.66 (dd, 1H, $J=2.5, 8.8$ Hz), 6.66 (d, 1H, $J=2.5$ Hz), 5.08 (b, 1H), 4.33 (t, 2H, $J=5.1$ Hz), 4.08 (d, 1H, $J=7.3$ Hz), 3.80 (s, 3H), 3.25 (m, 1H), 3.13 (q, 2H, $J=5.3$ Hz), 2.98 (s, 3H), 2.02-1.00 (m, 9H).

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Example 62

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(3-pyridyl)sulfonylamino)cyclohexylmethylamino-3-thia-benzo[e]azulene in 63% yield: m.p. 158-160 °C; 487 (ESMS, MH^+); 1H NMR (CDCl₃) δ 9.10 (d, 1H, $J=2.2$ Hz), 8.81 (dd, 1H, $J=1.5, 4.8$ Hz), 8.18 (apparent dt, 1H, $J = 4.1, 1.5$ Hz), 7.65 (dd, 1H, $J=2.8, 10.8$ Hz), 7.48 (dd, 1H, $J=4.8, 5.4$ Hz), 7.05 (dd, 1H, $J=5.9, 8.3$ Hz), 6.83 (apparent dt, 1H, $J=2.8, 8.2$ Hz), 5.06 (b, 1H), 4.59 (d, 1H, $J=7.7$ Hz), 3.19-3.00 (m, 1H), 3.10 (t, 2H, $J=6.1$ Hz), 2.85 (t, 2H, $J=3.4$ Hz), 2.80-2.76 (m, 2H), 2.10-0.80 (m, 9H).

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Example 63

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trans-1-Aza-4,5-dihydro-9-methoxy-2-{4-methylsulfonyl-amino)cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene in 54% yield: 438 (ESMS, MH^+); 1H NMR (CDCl₃) δ 7.80 (d, 1H, $J=3.2$ Hz), 6.92 (d, 1H, $J=8.7$ Hz), 6.72 (dd, 1H,

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J=3.2, 8.8 Hz), 5.04 (broad m, 1H), 4.28 (t, 2H, J=5.1 Hz), 4.12 (q, 2H, J=7.2 Hz), 4.11 (m, 1H), 3.83 (s, 3H), 3.40-3.13 (m, 5H), 2.99 (s, 3H), 2.20-1.00 (m, 9H); m.p. (HCl salt) 200-215 °C.

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Example 64

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-9-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine
10 as a gray solid: m.p. 165-170 °C; 452 (ESMS, MH⁺); ¹H NMR δ 1.1-1.3 (4H, m), 1.37 (3H, t, J = 7.4 Hz), 1.92 (2H, m), 2.12 (2H, m), 3.04 (2H, q, J = 7.4 Hz), 3.14 (4H, t, J = 5.2 Hz), 3.25 (1H, m), 3.83 (3H, s), 3.95 (1H, d, J = 8.1 Hz), 4.28 (2H, t, J = 5.2 Hz), 5.07 (1H, broad), 6.72 (1H,
15 dd, J = 3.1, 8.7 Hz), 6.92 (1H, d, J = 8.7 Hz), 7.79 (1H, d, J = 3.1 Hz).

Example 65

20 trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-7-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-amine hydrochloride as a beige solid: m.p. 225-230 °C; 438 (ESMS, MH⁺); ¹H NMR (free base) δ 1.10-1.30 (4H, m), 1.93 (2H, m), 2.15 (2H, m), 2.98 (3H, s), 3.16 (4H, m),
25 3.28 (1H, m), 3.88 (3H, s), 4.40 (2H, t, J = 5.2 Hz), 5.02 (1H, broad), 6.82 (1H, dd, J = 1.5, 8.0 Hz), 7.02 (1H, t, J = 8.1 Hz), 7.85 (1H, dd, J = 1.5, 8.1 Hz).

Example 66

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trans-1-Aza-4,5-dihydro-7-methoxy-2-{4-dimethylamino-sulfonylamino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene in 27% yield: 467 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.84 (dd, 1H, J=1.4, 8.1 Hz), 7.02 (apparent t,

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1H, J=8.1 Hz), 6.82 (dd, 1H, J=1.4, 8.0 Hz), 5.11 (m, 1H), 4.41-4.33 (m, 4H), 3.96 (d, 1H, J=8.0 Hz), 3.88 (s, 3H), 3.19-3.10 (m, 4H), 2.78 (s, 6H), 2.20-1.00 (m, 8H); m.p. (HCl salt) 206-208 °C.

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Example 67

trans-N2-(4-Dimethylphosphonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine as a yellow solid: m.p. 58-62 °C; CIMS m/e = 454 (MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 1.04 (4H, m), 1.48 (1H, broad), 1.80 (2H, m), 2.00 (2H, m), 2.10 (2H, m), 2.80 (6H, m), 3.04 (2H, m), 3.67 (3H, s), 3.71 (3H, s), 5.62 (1H, broad), 6.81 (1H, m), 7.04 (1H, m), 7.66 (1H, dd, J = 2.6, 10.8 Hz).

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Example 68

trans-N2-(4-Ethoxycarbonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine hydrochloride as a white solid: m.p. (HCl salt) 94-97 °C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.10 (4H, m), 1.23 (3H, t, J = 7.3 Hz), 1.57 (1H, m), 1.86 (2H, m), 2.04 (4H, m), 2.79 (2H, m), 2.86 (2H, t, J = 6.9 Hz), 3.11 (2H, t, J = 6.2 Hz), 3.44 (1H, m), 4.11 (2H, q, J = 7.2 Hz), 4.50 (1H, broad), 5.24 (1H, broad), 6.83 (1H, dt, J = 2.8, 8.2 Hz), 7.06 (1H, dd, J = 5.9, 8.3 Hz), 7.69 (1H, dd, J = 2.8, 10.8 Hz).

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Example 69

1-Aza-9-fluoro-4,5-dihydro-2-(2-(2-isopropylsulfonylamino)-ethoxy)ethylamino-3-thia-benzo[e]-azulene in 60% yield: m.p. (HCl salt) 50-55 °C; ¹H NMR (300 MHz,

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CDCl₃) δ 1.00 1.37 (d, 6H, J = 6.9 Hz), 2.08 (m, 2H),
2.75-2.90 (m, 4H), 3.18 (septet, 1H, J = 6.9 Hz), 3.33
(apparent q, 2H, J = 5.0 Hz), 3.53 (apparent q, 2H, J = 5.0
Hz), 3.61 (t, 2H, J = 5.0 Hz), 3.71 (t, 2H, J = 4.8 Hz), 4.68
5 (t, 1H, d, J = 5.5 Hz), 5.38 (1H, broad), 6.84 (1H, dt, J
= 2.8, 8.2 Hz), 7.07 (1H, dd, J = 5.9, 8.3 Hz), 7.70 (1H,
dd, J = 2.8, 10.8 Hz).

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Example 70

2-(4-Methylsulfonylaminoethyl)cyclohexylamino-4H-
chromeno[4,3-d]thiazole (hydrogen chloride salt) was
obtained as a blue-green solid in 64% yield: m.p. (HCl
15 salt) 140-144 °C; ¹H NMR (CDCl₃) δ 7.56 (dd, 1H, J = 1.3,
7.6 Hz), 7.13 (m, 1H), 6.96 (td, 1H, J = 0.9, 7.4 Hz),
6.88 (d, 1H, J = 7.4 Hz), 5.31 (m, 3H), 4.78 (t, 1H, J =
6.5 Hz), 3.27 (m, 1H), 2.99 (t, 2H, J = 6.6 Hz), 2.97 (s,
3H) 2.23 (m, 2H), 1.87 (m, 2H), 1.49 (m, 1H), 1.30-1.06
20 (m, 4H); 394 (ESMS, MH⁺).

Example 71

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methylsulfonyl-
amino)cyclohexylmethylamino-3-thia-benzo[e]azulene
25 (hydrogen chloride salt) was obtained as a yellow solid in
50% yield: m.p. (hydrogen chloride salt) 94-97 °C; ¹H NMR
(CD₃OD) δ 7.88 (d, 1H, J = 8.6 Hz), 6.78 (dd, 1H, J = 2.7,
8.8 Hz), 6.68 (d, 1H, J = 2.6 Hz), 5.21 (m, 1H), 4.23 (m,
1H), 3.81 (s, 3H), 3.25 (m, 1H), 3.11 (m, 2H), 2.98 (s,
30 3H), 2.83 (t, 2H, J = 7.0 Hz), 2.81 (m, 2H), 2.10 (m, 4H),
1.89 (m, 2H), 1.59 (m, 1H), 1.31-1.07 (m, 4H); 436 (ESMS,
MH⁺).

Example 72

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methyl-sulfonylamino-methyl)cyclohexylamino-3-thia-benzo[e]azulene was obtained as a yellow solid in 20% yield: m.p. 224-225 °C; ¹H NMR δ 7.87 (d, 1H, *J* = 8.7 Hz), 6.78 (dd, 1H, *J* = 2.7, 8.5 Hz), 6.68 (d, 1H, *J* = 2.5 Hz), 4.94 (m, 1H), 4.44 (m, 1H), 3.81 (s, 3H), 3.26 (m, 1H), 2.98 (m, 2H), 2.96 (s, 3H), 2.83 (m, 4H), 2.27 (m, 2H), 2.10 (m, 2H), 1.88 (m, 2H), 1.51 (m, 1H), 1.27-1.04 (m, 4H); 436 (ESMS, MH⁺).

Example 73

trans-1-Aza-4,5-dihydro-2-(4-isopropylsulfonyl-aminomethyl)-cyclohexylamino-8-methoxy-3-thia-benzo[e]-azulene (hydrogen chloride salt) was obtained as a light brown solid in 3.4% yield: m.p. (HCl salt) 87-89 °C; ¹H NMR (free base, CDCl₃) δ 7.87 (d, 1H, *J* = 8.4 Hz), 6.8 (dd, 1H, *J* = 2.7, 8.4 Hz), 6.69 (d, 1H, *J* = 2.7 Hz), 5.10 (b, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 3.29-3.12 (m, 2H), 2.98 (t, 2H, *J* = 6.6 Hz), 2.82 (m, 4H), 2.25 (m, 2H), 2.09 (m, 2H), 1.91 (m, 2H), 1.50 (m, 1H), 1.38 (d, 6H, *J* = 6.6 Hz), 1.30-1.03 (m, 4H); 464 (ESMS, MH⁺).

Example 74

trans-1-Aza-4,5-dihydro-2-(4-methylsulfonylamino-methyl)-cyclohexylamino-7-methoxy-3-thia-benzo[e]-azulene was obtained as a light yellow solid in 59% yield: ¹H NMR δ 7.75 (dd, 1H, *J* = 1.2, 8.0 Hz), 7.01 (t, 1H, *J* = 8.1 Hz), 6.81 (dd, 1H, *J* = 1.2, 7.0 Hz), 4.81 (m, 1H), 4.40 (t, 2H,

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$J = 5.1$ Hz), 4.34 (m, 1H), 3.88 (s, 3H), 3.34 (m, 1H), 3.18 (t, 2H, $J = 5.0$ Hz), 3.03 (t, 2H, $J = 7.0$ Hz), 2.97 (s, 3H), 2.28 (m, 2H), 1.91 (m, 2H), 1.50 (m, 1H), 1.30-1.08 (m, 4H); 438 (ESMS, MH^+).

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Example 75

trans-1-Aza-4,5-dihydro-2-(4-ethylcarbonylamino-methyl)-
10 cyclohexylamino-9-fluoro-3-thia-benzo[e]-azulene was
obtained as a light yellow solid in 87% yield: 1H NMR δ
7.69 (dd, 1H, $J = 2.7, 10.8$ Hz), 7.06 (dd, 1H, $J = 5.9,$
8.4 Hz), 6.83 (td, 1H, $J = 2.8, 8.2$ Hz), 5.50 (m, 1H),
4.82 (m, 1H), 3.29 (m, 1H), 3.15 (t, 2H, $J = 6.5$ Hz), 2.86
15 (t, 2H, $J = 6.9$ Hz), 2.79 (m, 2H), 2.21 (m, 4H), 2.07 (m,
2H), 1.84 (m, 2H), 1.51 (m, 1H), 1.29-1.03 (m, 4H), 1.17
(t, 3H, $J = 7.5$ Hz); 402 (ESMS, MH^+).

Example 76

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trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(4-morpholinyl)-
sulfonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene
(hydrogen chloride salt) was obtained as a light yellow
solid in 28% yield: 1H NMR (free base) δ 7.67 (dd, 1H, $J =$
25 2.8, 10.8 Hz), 7.06 (dd, 1H, $J = 5.9, 8.0$ Hz), 6.83 (td,
1H, $J = 2.7, 8.1$ Hz), 4.96 (d, 1H, $J = 8.0$ Hz), 4.59 (t,
1H, $J = 6.1$ Hz), 3.74 (m, 4H), 3.23 (m, 5H), 2.93 (t, 2H,
 $J = 4.8$ Hz), 2.86 (t, 2H, $J = 6.9$ Hz), 2.79 (m, 2H), 2.24
(m, 2H), 2.07 (m, 2H), 1.84 (m, 2H), 1.46 (m, 1H), 1.30-
30 1.02 (m, 4H); 495 (ESMS, MH^+).

Example 77

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-methoxy)-ethoxy-carbonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene
5 2-methoxyethyl N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-yl)amino]cyclohexyl)methyl}-carbamate:

tert-butyl N-[(4-{[(benzoylamino)carbothioyl]amino}-cyclo-
10 hexyl)methyl]carbamate: A solution of tert-butyl N-[(4-aminocyclohexyl)methyl]carbamate (4.683 g, 20.5 mmol) and benzoyl isothiocyanate (3.77 g, 23.1 mmol) in 180 ml THF was stirred at room temperature for 20 hours. The solvent was removed in vacuo to yield a golden viscous oil. The
15 oil was triturated with 250 ml hexane and the resulting solid was collected by filtration and washed with hexane. The off-white solid was washed several times with hexane and was dried under vacuum to yield 91% (7.32 g) of the desired product as an off-white solid: ¹H-NMR (CDCl₃) δ
20 1.20 (6H, m), 1.44 (9H, s), 1.83 (2H, m), 2.25 (2H, m), 3.01 (2H, t, J = 6.4 Hz), 4.20 (1H, m), 4.62 (1H, m), 7.51 (2H, t, J = 7.9 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.81 (2H, d, J = 7.2 Hz), 8.93 (1H, s); 392 (ESMS, MH⁺).

tert-butyl-N-({4-[(aminocarbothioyl)amino]-cyclohexyl}-
25 methyl)carbamate : A solution of tert-butyl-N-[(4-{[(benzoylamino)carbothioyl]amino}-cyclohexyl)methyl]carbamate (7.30 g, 18.6 mmol) in 110 ml MeOH was prepared. Then, a solution of potassium
30 carbonate (5.15 g, 37.3 mmol) in 50 ml water was added to the stirred solution. The solution was stirred at room temperature for 18 hours. The solvent was removed in vacuo and the residue was extracted several times with EtOH. The combined EtOH extracts were evaporated to

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dryness to yield 6.15 g of an off-white solid. The solid was re-dissolved in 200 ml acetone and stirred for 20 minutes. The solution was filtered by suction to remove the insoluble salts and the filtrate was evaporated to yield 98% (5.23g) of the desired product as a slightly yellow solid: $^1\text{H-NMR}$ (CDCl_3) δ 1.10 (6H, m), 1.43 (9H, s), 1.80 (2H, m), 2.10 (2H, m), 2.95 (2H, t, $J = 6.4$ Hz), 4.75 (1H, broad), 6.03 (2H, s), 6.64 (1H, broad); 288 (ESMS, MH^+).

10

6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5H-

benzo[a]cyclohepten-5-one: A solution of 8-fluoro-1-benzosuberone (20.00g, 112.2 mmol) in 125 ml glacial acetic acid was prepared. Bromine (5.80 ml, 113 mmol) was added dropwise with stirring. After addition was complete, the solution was poured into 400 ml water and extracted with EtOAc (500 ml). The EtOAc layer was separated and washed with 500 ml water. The organic layer was dried over MgSO_4 , filtered and evaporated to yield 100% (28.9 g) of the desired product as a viscous oil: $^1\text{H-NMR}$ (CDCl_3) δ 2.00 (2H, m), 2.33 (2H, m), 2.84 (1H, m), 3.00 (1H, m), 4.83 (1H, m), 7.13 (2H, m), 7.29 (1H, dd).

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tert-Butyl-N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta-[d][1,3]thiazol-2-yl)amino]-cyclohexyl)methyl}-carbamate: A solution of tert-butyl-N-({4-[(aminocarbothioyl)amino]cyclohexyl}-methyl)carbamate (22.4 g, 78.0 mmol), 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (20.1 g, 78.0 mmol), and 22.5 ml diisopropylethylamine in 260 ml absolute ethanol was heated at reflux for 3 hours. The solvent was removed in vacuo with gentle heating (~ 40 C). The resulting viscous golden oil was taken up into 400 ml EtOAc and washed with water (600 ml). The EtOAc layer was separated and

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evaporated to yield 39.0 g of a viscous golden oil. The oil was chromatographed on silica-gel eluting with EtOAc to yield 34.5 g of the desired product (99% yield):

¹H-NMR (CDCl₃) δ 1.18 (6H, h, J = 12.2 Hz), 1.44 (9H, s),
5 1.81 (2H, m), 2.22 (2H, m), 2.79 (2H, m), 2.86 (2H, t, J =
7.1 Hz), 3.00 (2H, t, J = 6.3 Hz), 3.25 (1H, broad), 4.62
(1H, broad), 4.86 (1H, broad), 6.83 (1H, dt, J = 2.9 Hz),
7.04 (1H, m), 7.70 (1H, dd, J = 2.8 Hz).

10 trans-N2-[4-(Aminomethyl)cyclohexyl]-9-fluoro-5,6-dihydro-
4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: A
solution of trans-tert-butyl N-({4-[(9-fluoro-5,6-dihydro-
4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-
yl)amino]cyclohexyl}-methyl)-carbamate (34.5 g, 77.0 mmol)
15 in 200 ml EtOAc and 100 ml 4N HCl in dioxane was stirred
at room temperature for 2 hours. The resulting solid was
collected by filtration and the solid product washed with
Et₂O and dried under vacuum to yield 25.9 g of the desired
product as a pale yellow solid. An additional 1.43g of
20 the product was obtained by allowing the filtrate to stand
in a closed flask for several days. The overall yield was
85%: ¹H-NMR (CD₃OD) δ 1.25 (2H, m), 1.51 (2H, m), 1.70 (1H,
broad), 1.95 (2H, m), 2.18 (4H, m), 2.80 (6H, m), 3.63
(1H, broad), 7.11 (1H, dt, J = 2.5Hz, 8.4 Hz), 7.36 (2H,
25 m); 346 (ESMS, MH⁺).

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-methoxy)-ethoxy-
carbonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene
2-methoxyethyl N-({4-[(9-fluoro-5,6-dihydro-4H-
30 benzo[6,7]cyclohepta[d][1,3]thiazol-2-
yl)amino]cyclohexyl}-methyl)carbamate: A solution trans-
N2-[4-(aminomethyl)-cyclohexyl]-9-fluoro-5,6-dihydro-4H-
benzo[6,7]cyclohepta-[d][1,3]thiazol-2-amine (0.30 g, 0.72
mmol) in anhydrous THF (3 ml) and triethylamine (1.0 ml)

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was flushed with nitrogen. The solution was stirred for 5 minutes and 0.095 ml chloroformic acid 2-methoxyethyl ester (0.114g, 0.82 mmol) was added dropwise to the stirring solution via syringe. The solution was stirred at room temperature for 2 hours. The solvent was removed in vacuo and the residue was chromatographed on silica-gel eluting with 1:1 EtOAc/Hexane to yield 25% (80 mg) of the desired product as a colorless viscous oil: ¹H-NMR (CDCl₃) δ 1.11 (4H, septet, J = 9.8 Hz), 1.42 (1H, broad), 1.80 (2H, m), 2.04 (2H, m), 2.20 (2H, m), 2.77 (2H, m), 2.84 (2H, t, J = 6.9 Hz), 3.04 (2H, t, J = 6.4 Hz), 3.24 (1H, broad), 3.38 (3H, s), 3.58 (2H, m), 4.22 (2H, m), 4.90 (1H, broad), 5.00 (1H, d), 6.81 (1H, dt, J = 2.8 Hz), 7.03 (1H, m), 7.68 (1H, dd, J = 2.7 Hz, 10.9 Hz); 448 (ESMS, MH⁺).

Example 78

trans-N2-(4-(1-Morpholinylsulfonylaminomethyl)-cyclohexyl-8-methoxy-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-amine hydrochloride: Prepared from *trans*-N2-(4-aminomethyl)cyclohexyl-8-methoxy-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine and 1-morpholinylsulfonyl chloride as a light brown solid: m.p. 130-132 °C; 507 (ESMS, MH⁺); ¹H NMR (free base) δ 7.88 (dd, 1H, J = 0.4, 8.7 Hz), 6.78 (dd, 1H, J = 2.4, 8.8 Hz), 6.68 (d, 1H, J = 2.3 Hz), 4.85 (m, 1H), 4.25 (m, 1H), 3.81 (s, 3H), 3.73 (m, 4H), 3.30 (m, 1H), 3.25 (m, 4H), 2.96 (m, 2H), 2.81 (m, 4H), 2.26 (m, 2H), 2.10 (m, 2H), 1.87 (m, 2H), 1.49 (m, 1H), 1.30-1.03 (m, 4H).

Example 79

3-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-yl)amino]cyclohexyl)methyl)-1,3-
5 oxazolan-2-one:

2-chloroethyl-N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-
cyclohepta[d][1,3]thiazol-2-yl)amino]-cyclohexyl)methyl)-
carbamate: A solution of trans-N2-[4-
10 (aminomethyl)cyclohexyl]-9-fluoro-5,6-dihydro-4H-benzo-
[6,7]cyclohepta[d][1,3]thiazol-2-amine (5.00 g, 11.95
mmol), 20 ml anhydrous pyridine, and 8 ml
diisopropylethylamine was stirred under N₂. Then 2-
chloroethyl chloroformate (1.40 ml, 13.6 mmol) was added
15 dropwise to the stirring solution. The solution was
stirred at room temperature for 2 hours and then poured
into 250 ml water and extracted with 250 ml EtOAc. The
extract was separated and evaporated to yield 100% (5.40
g) of the desired product as a highly viscous golden oil:
20 ¹H-NMR (CDCl₃) δ 1.13 (3H, m), 1.43 (1H, m), 1.82 (2H, m),
2.06 (2H, m), 2.22 (2H, m), 2.81 (4H, m), 3.06 (2H, t, J =
6.4 Hz), 3.25 (1H, m), 3.70 (3H, m), 4.31 (2H, t, J = 5.7
Hz), 4.89 (2H, m), 6.82 (1H, t, J = 2.8 Hz), 7.04 (1H, m),
7.70 (1H, dd, J = 2.7, 10.8 Hz); 452 (ESMS, MH⁺).

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3-({4-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-yl)amino]cyclohexyl)methyl)-1,3-
oxazolan-2-one: To a stirred solution of 2-chloroethyl-N-
({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-
30 cyclohepta[d][1,3]thiazol-2-yl)amino]-
cyclohexyl)methyl)carbamate (5.4 g, 11.95 mmol) in 100 ml
anhydrous DMF was added NaH (60% in mineral oil) (0.6 g,
15.0 mmol). TLC (EtOAc) indicated that the reaction had
proceeded to approximately 40% completion after 15

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minutes. An additional 0.58g (14.5 mmol) NaH (60% in mineral oil) was added and the solution was stirred at room temperature for another 15 minutes. TLC indicated the reaction was complete. The solution was poured into water (500 ml) and was extracted with EtOAc. The extract was separated and evaporated to yield a dark viscous oil. The oil was chromatographed on silica-gel eluting with 2:1 EtOAc/hexane to yield a white solid. The solid was dissolved in 40 ml CHCl₃ and 10 ml 1N HCl in Et₂O was added to the solution. The volatiles were removed and the resulting solid was triturated with Et₂O. The solution was filtered and the slightly tan solid washed with ether and dried to yield 52% (2.83 g) of the desired product as the HCl salt: ¹H-NMR (Free-base) (CDCl₃) δ 1.16 (4H, m), 1.60 (1H, m), 1.80 (2H, m), 2.05 (2H, m), 2.22 (2H, m), 2.81 (4H, m), 3.12 (2H, d, J = 7.3Hz), 3.27 (1H, m), 3.57 (2H, t, J = 8.2 Hz), 4.33 (2H, t, J = 8.0 Hz), 5.05 (1H, d, J = 7.7 Hz), 6.83 (1H, dt, J = 2.7, 8.2 Hz), 7.05 (1H, m), 7.68 (1H, dd, J = 2.7, 10.8 Hz). m.p. (HCl salt) 223-225 °C. Anal. Calcd. For C₂₂H₂₇N₃ClFO₂S: C, 58.5; H, 6.0; N, 9.3. Found: C, 58.43; H, 6.06; N, 9.38; 416 (ESMS, MH⁺).

Example 80

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-yl)amino]cyclohexyl}-methyl)-2-methoxyacetamide: To a stirred, septum capped solution of trans-N2-[4-(aminomethyl)-cyclohexyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-amine (5.00g, 11.95 mmol) in anhydrous pyridine (20 ml) and diisopropylethylamine (10 ml) was added methoxyacetyl chloride (1.20 ml, 13.1 mmol) dropwise. The solution was stirred at room temperature for 2 hours and was then poured into 250 ml water and extracted with 250 ml EtOAc.

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The extract was evaporated to yield a golden viscous oil which was chromatographed on silica-gel eluting with EtOAc to yield 88% (4.40 g) of the desired product as a slightly yellow solid. A small portion of the product was recrystallized from EtOAc (m.p. 95-97 °C). The free-base was dissolved in 60 ml CHCl₃ and converted to its HCl salt by adding 14.0 ml 1.0 N HCl in ether followed by evaporation of the solvent. The resulting foam was stirred with ether (75 ml), filtered and washed with ether to yield the HCl salt as a solid: ¹H-NMR (Free-base) (CDCl₃) δ 1.12 (4H, m), 1.45 (1H, m), 1.81 (2H, m), 2.05 (2H, m), 2.21 (2H, m), 2.80 (4H, m), 3.16 (2H, t, J = 6.5 Hz), 3.25 (1H, m), 3.41 (3H, s), 3.89 (2H, s), 5.03 (1H, d, J = 8.0 Hz), 6.62 (1H, broad t), 6.81 (1H, dt, J = 2.9, 8.3 Hz), 7.03 (1H, m), 7.69 (1H, dd, J = 2.8, 10.8 Hz). m.p. 63-65 °C. Anal. Calcd. For C₂₂H₂₉N₃O₂SFCl+0.5CHCl₃: C, 52.61; H, 5.79; N, 8.18. Found: C, 52.61; H, 5.92; N, 8.08; 418 (ESMS, MH⁺).

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Example 81

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta-[d][1,3]thiazol-2-yl)amino]cyclohexyl}-methyl)acetamide:
To a stirred, septum capped solution of trans-N2-[4-(aminomethyl)cyclohexyl]-9-fluoro-5,6-dihydro-4H-benzo-[6,7]cyclohepta-[d][1,3]thiazol-2-amine (0.165 g, 0.394 mmol) in 3.0 ml anhydrous pyridine was added 0.034 ml (0.038 g, 0.48 mmol) acetyl chloride dropwise. Stirring at room temperature was continued for 90 minutes and the solution was then poured into 50 ml water and extracted with EtOAc (2X50 ml). The combined extracts were evaporated to yield 0.126 g of the crude product as a viscous golden oil. The oil was chromatographed on preparative TLC eluting with EtOAc to yield 28% (0.042 g)

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of the desired product as a white solid: ^1H -NMR (CDCl_3)
 δ 1.13 (4H, m), 1.43 (1H, m), 1.80 (2H, m), 1.98 (3H, s),
2.05 (2H, m), 2.21 (2H, m), 2.80 (4H, m), 3.10 (2H, t, J =
6.5 Hz), 3.24 (1H, m), 5.00 (1H, d, J = 7.8 Hz), 5.75 (1H,
5 m), 6.81 (1H, dt, J = 2.8, 8.2 Hz), 7.04 (1H, m), 7.69
(1H, dd, J = 2.7, 10.8 Hz); m.p. 88-91°C.

Example 82

10 trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-propyl-
formamido)-methyl)cyclohexylamino-3-thia-benzo[e]-azulene
(hydrogen chloride salt) was obtained as a yellow solid in
54% yield: ^1H NMR (free base) δ 8.10 (s, 0.5H), 8.00 (s,
0.5H), 7.68 (m, 1H), 7.04 (m, 1H), 6.83 (m, 1H), 5.07 (m,
15 1H), 3.31-3.02 (m, 5H), 2.85 (m, 4H), 2.23 (m, 2H), 2.05
(m, 2H), 1.77 (m, 2H), 1.58 (m, 3H), 1.26-0.87 (m, 7H);
416 (ESMS, MH^+).

Example 83

20 trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-isopropyl-
formamido)methyl)cyclohexylamino-3-thia-benzo[e]-azulene
(hydrogen chloride salt) was obtained as a yellow solid in
48% yield: m.p. (HCl salt) 106-107 °C; ^1H NMR (CD_3OD) δ
25 8.22 (s, 0.6H), 7.98 (s, 0.4H), 7.37 (m, 2H), 7.12 (m,
1H), 4.18 (m, 0.4H), 3.73 (m, 0.6H), 3.60 (m, 1H), 3.17
(m, 2H), 2.78 (m, 4H), 2.19 (m, 4H), 1.86 (m, 2H), 1.74
(m, 1H), 1.41 (m, 2H), 1.32 (d, 4H), 1.31 (d, 2H), 1.17
(m, 2H); 416 (ESMS, MH^+).

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Example 84

$\text{N1}-\{4-[(4,5\text{-dihydrobenzo}[2,3]\text{oxepino}[4,5\text{-d}][1,3]\text{thiazol-2-ylamino)methyl}] \text{cyclohexyl}\}-2\text{-methoxyacetamide:}$

Benzyl-N-[4-({[(benzoylamino)carbothioyl]amino}-methyl)-cyclohexyl]carbamate: A solution of benzyl N-[4-(aminomethyl)cyclohexyl]carbamate HCl (3.46 g, 11.6 mmol) and diisopropylethylamine (6.0 ml) in anhydrous THF (90 ml) was stirred at room temperature for 20 minutes. To this solution was added benzoylisothiocyanate (2.00 g, 12.3 mmol) and the reaction mixture stirred at room temperature for 14 hours. The solution was poured into water (200 ml) and extracted with Et₂O (2X150 ml). The organic layer was dried over MgSO₄, filtered and evaporated to yield a solid. The solid was triturated with hexane and filtered to yield 99% (5.023g) of the desired product.

Benzyl-N-(4-{[(aminocarbothioyl)amino]methyl}-cyclohexyl)-carbamate: To a solution of benzyl N-[4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexyl]carbamate (5.023 g, 11.4 mmol) in MeOH (110 ml) was added a solution of K₂CO₃ (3.5 g, 25.3 mmol) in water (30 ml). The solution was stirred for 24 hours at room temperature and the solvent was removed in vacuo with repeated additions of MeOH to azeotropically remove water. The resulting solid was treated with acetone (60 ml) and filtered. The filtrate was evaporated to yield 95% (3.47 g) of a yellow solid.

Benzyl-N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}-carbamate: A solution containing benzyl N-(4-{[(aminocarbothioyl)amino]methyl}-cyclohexyl)-carbamate (3.45 g, 10.73 mmol), 4-bromo-2,3,4,5-tetrahydro-1-benzoxepin-5-one (2.60 g, 10.78 mmol), diisopropylethylamine (2.50 ml) and EtOH (50 ml) was heated at reflux for 4 hours. The solvent was removed and

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the residue was chromatographed on silica-gel eluting with 1:3 EtOAc/Hexane to yield 65% (3.2 g) of the product as a white solid: m.p. 124-127 °C; ¹H-NMR (CDCl₃) δ 1.09 (4H, pentet, J = 10.4 Hz), 1.55 (1H, broad), 1.83 (2H, m), 2.04 (2H, broad), 3.10 (2H, t, J = 6.2 Hz), 3.15 (2H, t, J = 5.2 Hz), 3.43 (1H, broad) 4.33 (2H, t, J = 5.2 Hz), 4.62 (1H, d, J = 8.0 Hz), 5.08 (2H, s), 5.31 (1H, m), 7.00 (1H, dd, J = 1.2 Hz, 7.8 Hz), 7.12 (2H, m), 7.35 (5H, s), 8.25 (1H, dd, J = 1.7 Hz, 7.8 Hz); 464 (ESMS, MH⁺).

N₂-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine: A solution containing benzyl-N-{4-[(4,5-dihydrobenzo [2,3]oxepino[4,5-d]-[1,3]-thiazol-2-ylamino)methyl]-cyclohexyl}carbamate (3.00 g, 6.47 mmol), glacial acetic acid (50 ml) and conc. HCl (20 ml) was heated to a gentle reflux for 45 minutes. The solvent was removed on the rotor-vap with gentle heating and the residue diluted with 150 ml water. The resulting solution was made basic with NaOH (pH~11). At this point, much of the product precipitated out of solution and stuck to the sides of the flask. EtOAc (200 ml) was added and the solution was shaken vigorously. The phases were separated and the aqueous phase extracted with EtOAc. The combined extracts were washed with water and evaporated to yield 2.30 g of a brown viscous oil. The oil was taken up into 40 ml EtOAc and 5 ml 4M HCl in dioxane added. The resulting dihydrochloride salt was obtained by filtration and washed with EtOAc and then several times with ether. Upon drying, 100% (2.6 g) of the salt was obtained as a slightly tan free-flowing solid: ¹H-NMR (d₄-MeOH) δ 1.21 (2H, m), 1.43 (2H, m), 1.79 (1H, m), 1.99 (2H, m), 2.10 (2H, m), 3.09 (1H, m), 3.18 (2H, t, J = 5.0 Hz), 3.35 (2H, d, J = 6.7 Hz), 4.32 (2H, t, J = 5.3 Hz), 7.12 (1H, dd, J

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= 1.1, 8.0 Hz), 7.22 (1H, m), 7.33 (1H, m), 7.70 (1H, dd, J = 1.3, 8.0 Hz); 330 (ESMS, MH⁺).

To a stirred solution of N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]oxepino-[4,5-d][1,3]thiazol-2-amine (0.600 g, 1.49 mmol), anhydrous pyridine (3 ml), and diisopropylethylamine (3 ml) was added methoxyacetyl chloride (0.163 ml, 1.78 mmol) dropwise. The solution was stirred for 30 minutes at room temperature and then poured into water (60 ml) and extracted with EtOAc. The extract was evaporated and the residue chromatographed on silica-gel eluting with EtOAc to yield 79% (470 mg) of the product as a white solid. The product was dissolved in chloroform and converted to its HCl salt with 1N HCl in Et₂O to yield 522 mg of the salt as a white solid: m.p. (HCl salt) 234-237°C; ¹H-NMR (free base, CDCl₃) δ 1.20 (4H, m), 1.80 (2H, broad), 2.00 (4H, m), 3.13 (4H, t, J = 5.0 Hz), 3.40 (3H, s), 3.79 (1H, broad), 3.86 (2H, s), 4.34 (2H, t, J = 5.1 Hz), 6.35 (1H, d), 7.05 (1H, dd, J = 1.3 Hz, 7.7 Hz), 7.28 (2H, m), 7.99 (1H, d, J = 8.3 Hz); 402 (ESMS, MH⁺).

Example 85

N-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)cyclohexyl)methyl]-N-propylformamide:

N1-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl)methyl]-propanamide: To a stirred solution of N2-[4-(aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine (0.600 g, 1.49 mmol) in anhydrous pyridine (3 ml) and diisopropylethylamine (3 ml) was added propionyl chloride (0.144 ml, 1.66 mmol) dropwise. The solution was stirred

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for 20 minutes at room temperature and then poured into water (50 ml) and extracted with EtOAc. The solvent was removed and the residue chromatographed on silica-gel eluting with EtOAc to yield 70% (402 mg) of the product as a light yellow solid: ¹H-NMR (CDCl₃) δ 1.12 (6H, m), 1.50 (1H, m), 1.65 (1H, m), 1.85 (2H, d, J = 12.1 Hz), 2.22 (4H, m), 3.16 (4H, t, J = 5.3 Hz), 3.32 (1H, m), 4.33 (2H, t, J = 5.2 Hz), 4.81 (1H, m), 5.49 (1H, m), 7.00 (1H, d, J = 8.5 Hz), 7.15 (2H, m), 8.25 (1H, d, J = 8.1 Hz). m.p. 56-60°C. FAB+ m/z = 386 (MH⁺).

N2-{4-[(Propylamino)methyl]cyclohexyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: To a solution of N1-{[4-(4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]-methyl}propanamide (0.380 g, 0.944 mmol) in anhydrous THF (7 ml) was added 1M BH₃ in THF (2.0 ml, 2.0 mmol). The solution was stirred for several hours at room temperature. TLC (EtOAc) indicated reaction to be incomplete and an additional 2.5 ml 1M BH₃ in THF was added to the solution which was then stirred overnight. 4N HCl (25 ml) was slowly added to the stirred solution and the solution was washed with EtOAc. The aqueous layer was made basic by addition of 20% NaOH. The resulting solution was extracted with EtOAc and the extract washed with water. Upon removal of the solvent, 72% (254 mg) of the product was obtained as a white solid: ¹H-NMR (CDCl₃) δ 0.88 (3H, t, J = 7.3 Hz), 1.12 (4H, m), 1.43 (3H, m), 1.75 (2H, m), 2.14 (2H, m), 2.41 (2H, d, J = 6.6 Hz), 2.51 (2H, t, J = 7.4 Hz), 2.60 (1H, m), 3.10 (2H, t, J = 5.0 Hz), 3.22 (1H, m), 4.27 (2H, t, J = 5.0 Hz), 5.35 (1H, m), 6.95 (1H, d, J = 7.6 Hz), 7.06 (2H, m), 8.20 (1H, d, J = 7.3 Hz); 372 (ESMS, MH⁺).

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N-{[4-(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-N-propylformamide: To a solution of N2-{4-[(propyl-amino)methyl]cyclohexyl}-4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine (0.254 g, 0.68 mmol) in anhydrous THF (4 ml) was added 1H-benzotriazole-1-carboxaldehyde (0.110 g, 0.75 mmol). The solution was stirred at room temperature for 1 hour and then poured into 2N NaOH (50 ml) and extracted with EtOAc (60 ml). The extract was separated and evaporated to yield 295 mg of a viscous oil. Chromatography on silica-gel eluting with 1:1 EtOAc/hexane yielded 56% (152 mg) of the product as a white solid: ¹H-NMR (CDCl₃) δ 0.90 (3H, m), 1.14 (4H, m), 1.58 (2H, m), 1.78 (2H, m), 2.23 (2H, m), 3.20 (8H, m), 4.32 (2H, t, J = 4.9 Hz), 5.03 (1H, m), 6.99 (1H, m), 7.12 (2H, m), 8.01 (0.5H, s), 8.11 (0.5H, s), 8.22 (1H, d); m.p. 53-55 °C; 400 (ESMS, MH⁺).

Example 86

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N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxyethyl)formamide

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N2-({4-[(2-methoxyethyl)amino]cyclohexyl}methyl)-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: To a stirred solution of N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)-methyl]cyclohexyl}-2-methoxyacetamide (free-base) (0.450g, 1.12 mmol) in anhydrous THF (5 ml) was added 5.0 ml 1M BH₃ in THF (5.0 mmol). The solution was stirred at room temperature for 26 hours. 4N HCl (12 ml) was slowly added to the stirred solution and stirred continued for 1 hour. The solution was made basic with 2N NaOH (pH-9) and was extracted with EtOAc. Upon evaporation of the solvent,

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90% (390 mg) of the desired amine was obtained as a highly viscous colorless oil. The compound was converted to its dihydrochloride salt in chloroform with 1N HCl in Et₂O. Evaporation of the solvent gave 460 mg of the salt as a slightly hygroscopic white solid: m.p. 243-245°C (dec); ¹H-NMR (CDCl₃) δ 1.08 (4H, t, J = 10.8 Hz), 1.6 (2H, broad), 1.91 (4H, m), 2.41 (1H, broad), 2.80 (2H, t, J = 4.9 Hz), 3.15 (4H, m), 3.35 (3H, s), 3.49 (2H, t, J = 5.3 Hz), 4.32 (2H, t, J = 5.4 Hz), 5.13 (1H, broad t), 6.98 (1H, dd, J = 1.3 Hz, 7.7 Hz), 7.12 (2H, m), 8.24 (1H, dd, J = 1.6 Hz, 7.9 Hz); 388 (ESMS, MH⁺).

N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxy-ethyl)formamide:
To a stirred solution of N2-({4-[(2-methoxyethyl)amino]cyclohexyl)methyl}-4,5-dihydro-benzo-[2,3]oxepino[4,5-d][1,3]thiazol-2-amine (free-base) (0.356 g, 0.92 mmol) in anhydrous THF (4 ml) was added 1H-benzotriazole-1-carboxaldehyde (0.144 g, 0.98 mmol). The solution was stirred for 5 minutes at room temperature and TLC (EtOAc) indicated reaction to be complete. The solution was poured into 2N NaOH (50 ml) and extracted with EtOAc (60 ml). The extract was evaporated to yield 420 mg of the crude product as a white solid. The product was chromatographed on silica-gel eluting with 3:1 EtOAc/hexane to yield 78% (300 mg) of a white solid. The material was converted to its HCl salt in chloroform with 1M HCl in Et₂O. Upon evaporation of the solvent, a white hygroscopic solid was obtained. The solid was triturated with hexane, filtered and dried to yield 330 mg of a non-hygroscopic free flowing white solid: m.p. 164-166°C; ¹H-NMR (CDCl₃) δ 1.11 (2H, p), 1.53 (3H, m), 1.90 (5H, m), 3.14 (4H, m), 3.32 (3H, s), 3.43 (4H, m), 4.34 (2H, t),

5.43 (1H, broad), 7.00 (1H, ¹⁴⁶d), 7.12 (2H, m), 8.08 (0.4H, s), 8.18 (0.6H, s), 8.24 (1H, dd); 416 (ESMS, MH⁺).

Example 87

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trans-1-Aza-2-(4-(n-(ethyl)formamido)cyclohexyl)methyl-amino-4,5-dihydro-6-oxa-3-thia-benzo[e]azulene:

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trans-2-(4-Acetamido)cyclohexylmethylamino-1-aza-4,5-dihydro-6-oxa-3-thia-benzo[e]azulene:

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Benzyl-N-[4-({[(benzoylamino)carbothioyl]amino}-methyl)-cyclohexyl]carbamate: A solution of benzyl N-[4-(aminomethyl)cyclohexyl]carbamate HCl (3.46 g, 11.58 mmol) and diisopropylethylamine (6.0 ml) in anhydrous THF (90 ml) was stirred at room temperature for 20 minutes. To this solution was added benzoylisothiocyanate (2.00 g, 12.3 mmol). The solution was stirred at room temperature for 14 hours, poured into water (200 ml) and then extracted with Et₂O (2X150 ml). The organic layer was dried over MgSO₄, filtered and evaporated to yield a solid. The solid was triturated with hexane and filtered to yield 99% (5.023g) of the desired product.

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Benzyl-N-(4-{[(aminocarbothioyl)amino]methyl}-cyclohexyl)-carbamate: To a solution of benzyl N-[4-({[(benzoylamino)carbothioyl]amino}methyl)cyclohexyl]carbamate (5.02 g, 11.4 mmol) in MeOH (110 ml) was added a solution of K₂CO₃ (3.5 g, 25.3 mmol) in water (30 ml). The solution was stirred for 24 hours at room temperature. The solvent was removed in vacuo with repeated additions of MeOH to azeotropically remove water. The resulting solid was treated with acetone (60 ml) and filtered. The filtrate was evaporated to yield 95% (3.47 g) of a yellow solid.

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Benzyl-N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}-carbamate: A solution containing benzyl N-(4-
5 {[(aminocarbothioyl)amino]methyl}-cyclohexyl)-carbamate (3.45 g, 10.73 mmol), 4-bromo-2,3,4,5-tetrahydro-1-benzoxepin-5-one (2.60 g, 10.78 mmol), and diisopropylethylamine (2.50 ml) in EtOH (50 ml) was heated at reflux for 4 hours. The solvent was removed and the
10 residue was chromatographed on silica gel eluting with 1:3 EtOAc/hexane to yield 65% (3.2 g) of the product as a white solid: m.p. 124-127°C; ¹H-NMR (CDCl₃) δ 1.09 (4H, pentet, J = 10.4 Hz), 1.55 (1H, broad), 1.83 (2H, m), 2.04 (2H, broad), 3.10 (2H, t, J = 6.2 Hz), 3.15 (2H, t, J =
15 5.2 Hz), 3.43 (1H, broad) 4.33 (2H, t, J = 5.2 Hz), 4.62 (1H, d, J = 8.0 Hz), 5.08 (2H, s), 5.31 (1H, m), 7.00 (1H, dd, J = 1.2 Hz, 7.8 Hz), 7.12 (2H, m), 7.35 (5H, s), 8.25 (1H, dd, J = 1.7 Hz, 7.8 Hz). ESIMS m/z = 464 (MH⁺).

20 N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine: A solution of benzyl-N-{4-[(4,5-dihydrobenzo-[2,3]oxepino-[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}carbamate (3.00 g, 6.47 mmol) in glacial acetic acid (50 ml) and conc. HCl (20 ml) was
25 heated to a gentle reflux for 45 minutes. The solvent was removed on the rotor-vap with gentle heating and the residue diluted with water (150 ml). The resulting solution was made basic with NaOH (pH~11). EtOAc (200 ml) was added and the solution was shaken vigorously. The
30 phases were separated and the aqueous phase was extracted with EtOAc. The combined extract was washed with water and evaporated to yield 2.30 g of a brown viscous oil. The oil was taken up into 40 ml EtOAc and 5 ml 4N HCl in dioxane was added. The resulting dihydrochloride salt was

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obtained by filtration and washed with EtOAc and ether. Upon drying, 100% (2.6 g) of the salt was obtained as a tan solid: $^1\text{H-NMR}$ ($\text{d}_4\text{-MeOH}$) δ 1.21 (2H, m), 1.43 (2H, m), 1.79 (1H, m), 1.99 (2H, m), 2.10 (2H, m), 3.09 (1H, m), 3.18 (2H, t, $J = 5.0$ Hz), 3.35 (2H, d, $J = 6.7$ Hz), 4.32 (2H, t, $J = 5.3$ Hz), 7.12 (1H, dd, $J = 1.1, 8.0$ Hz), 7.22 (1H, m), 7.33 (1H, m), 7.70 (1H, dd, $J = 1.3, 8.0$ Hz). ESIMS $m/z = 330$ (MH^+).

10 N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}acetamide: To a stirred solution of N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine (0.600 g, 1.49 mmol) in anhydrous pyridine (3 ml) and
15 diisopropylethylamine was added acetyl chloride (0.130 ml, 1.83 mmol) dropwise. The solution was stirred for 30 minutes at room temperature and then poured into water (60 ml). The mixture was extracted with EtOAc, and the organic phase evaporated to afford a residue that was
20 chromatographed on silica-gel eluting with EtOAc to yield 72% (400 mg) of the desired product as a light yellow solid: m.p. 69-72°C. $^1\text{H-NMR}$ (CDCl_3) δ 1.11 (4H, m), 1.60 (1H, broad), 1.73 (1H, broad), 1.83 (2H, m), 1.95 (3H, s), 2.05 (2H, m), 3.14 (4H, m), 3.73 (1H, broad), 4.33 (2H, t, $J = 4.9$ Hz), 5.30 (1H, broad), 7.00 (1H, dd, $J = 0.9$ Hz, 7.7 Hz), 7.12 (2H, m), 8.24 (1H, dd, $J = 0.9$ Hz, 7.8 Hz). ESIMS $m/z = 372$ (MH^+).

30 N2-{[4-(Ethylamino)cyclohexyl)methyl]-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: To a stirred solution of N1-{4-[(4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)-methyl]cyclohexyl}acetamide (0.380 g, 1.02 mmol) in anhydrous THF (4 ml) was added 1M BH_3 in THF (5.0 ml, 5.0 mmol). The solution was stirred at

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room temperature overnight. 4N HCl (12 ml) was added slowly and stirring continued for 15 minutes. The resulting solution was made basic (pH~9) with 2N NaOH. The cloudy solution was extracted with EtOAc and the organic layer washed with water. Removal of the solvent in vacuo, gave 69% (252 mg) of the product as a solid which was used without further purification: ¹H-NMR (CDCl₃) δ 0.96 (4H, m), 1.08 (3H, t, J = 7.1 Hz), 1.47 (1H, m), 1.76 (2H, d, J = 12.1 Hz), 1.90 (2H, m), 2.37 (2H, m), 2.63 (2H, q, J = 7.0 Hz), 3.05 (2H, t, J = 5.7 Hz), 3.11 (2H, t, J = 5.1 Hz), 4.28 (2H, t, J = 5.2 Hz), 5.73 (1H, broad t), 6.96 (1H, dd, J = 0.9 Hz, 7.7Hz), 7.10 (2H, m), 8.22 (1H, dd, J = 1.3 Hz, 7.6 Hz); 358 (ESMS, MH⁺).

15 N-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-ethylformamide: To a stirred solution of N2-{[4-(ethylamino)cyclohexyl]methyl}-4,5-dihydrobenzo[2,3]-oxepino-[4,5-d][1,3]-thiazol-2-amine (0.252 g, 0.70 mmol) in anhydrous THF (3.5 ml) was added 20 1H-benzotriazole-1-carboxaldehyde (0.112 g, 0.76 mmol). The solution was stirred at room temperature for 1 hour and then poured into 2N NaOH (60 ml). The mixture was extracted with EtOAc and evaporated to afford 268 mg of the desired crude product as a solid. The product was 25 chromatographed on silica-gel eluting with 70% EtOAc/30% hexane to yield 56% (150 mg) of a white solid. The compound was dissolved in chloroform and converted to its HCl salt by addition of 1N HCl in ether. The solvents were removed in vacuo and the residue triturated with 30 hexane/ether and filtered to afford the product as a white solid: m.p. 210-213°C; ¹H-NMR (CDCl₃) δ 1.13 (4H, m), 1.59 (2H, m), 1.88 (6H, m), 3.17 (4H, m), 3.24 (3H, m), 4.32 (2H, t), 5.40 (1H, broad), 7.00 (1H, d), 7.13 (2H,

m), 8.09 (0.4H, s), 8.12¹⁵⁰ (0.6H, s), 8.23 (1H, dd);
386 (ESMS, MH⁺).

Example 88

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N-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}-N-propyl-formamide:

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N1-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-propanamide: To a stirred solution of N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]oxepino-[4,5-d][1,3]thiazol-2-amine (0.600 g, 1.49 mmol) in anhydrous pyridine (3 ml) and diisopropylethylamine (3 ml) was added propionyl chloride (0.155 ml, 1.78 mmol) dropwise. The solution was stirred for 1 hour at room temperature and poured into water (60 ml). The solution was extracted with EtOAc and the solvent removed *in vacuo* to yield a viscous golden oil. The oil was chromatographed on silica-gel eluting with 70% EtOAc/30% hexane to yield 74% (425 mg) of an orange solid: m.p. 70-73°C. ¹H-NMR (CDCl₃) δ 1.10 (6H, m), 1.60 (1H, broad), 1.83 (3H, m), 2.00 (3H, m), 2.17 (2H, q, J = 7.6 Hz), 3.13 (4H, q, J = 5.1 Hz), 3.73 (1H, broad), 4.32 (2H, t, J = 5.3 Hz), 5.32 (1H, broad), 7.00 (1H, dd, J = 6.4 Hz). ESIMS m/z = 386 (MH⁺).

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N2-{[4-(propylamino)cyclohexyl]methyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d][1,3]thiazol-2-amine: To a stirred solution of N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}propanamide (0.405 g, 1.05 mmol) in anhydrous THF (4 ml) was added 1M BH₃ in THF (5.5 ml, 5.5 mmol). The solution was stirred at room temperature for 52 hours. 4N HCl (12 ml) was added slowly and stirring continued for 30 minutes thereafter.

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The solution was poured into 2N NaOH (60 ml) and extracted with EtOAc. The extract was washed with 10% brine, separated and evaporated to yield 77% (300 mg) of the amine as a viscous golden oil: $^1\text{H-NMR}$ (CDCl_3) δ 0.88 (3H, t), 1.06 (2H, m), 1.38 (2H, m), 1.49 (2H, m), 1.80 (6H, m), 2.40 (1H, m), 2.58 (2H, t), 3.15 (2H, m), 3.63 (2H, t), 4.30 (2H, t), 5.12 (1H, m), 6.98 (1H, d), 7.11 (2H, m), 8.23 (1H, dd); 400 (ESMS, MH^+).

10 N-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-propylformamide: To a stirred solution of N2-{4-(propylamino)cyclohexyl}methyl}-4,5-dihydrobenzo-[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine (0.300 g, 0.81 mmol) in
15 anhydrous THF (4 ml) was added 1H-benzotriazole-1-carboxaldehyde (0.126 g, 0.86 mmol). The solution was stirred for 1 hour at room temperature and poured into 2N NaOH (50 ml). The mixture was extracted with EtOAc (60 ml). The extract was evaporated to yield 320 mg of the
20 crude product as a viscous yellow oil. The oil was chromatographed on silica-gel eluting with 70% EtOAc/30% hexane to afford 125 mg of the product as a colorless oil. The oil was dissolved in chloroform and converted to its HCl salt with 1N HCl in Et_2O . Upon evaporation of the
25 solvent, a solid was obtained. The solid was triturated with EtOAc, filtered and washed with hexane to give 25% (87mg) of the desired product as a white solid: m.p. (HCl salt) 195-197°C; $^1\text{H-NMR}$ (CDCl_3) δ 0.89 (3H, t), 1.05 (2H, p), 1.50 (5H, m), 1.79 (4H, m), 3.10 (6H, m), 4.30 (2H, m), 5.93 (2H, m), 7.06 (3H, m), 8.02 (0.4H, s), 8.10
30 (0.6H, s), 8.22 (1H, dd); 400 (ESMS, MH^+).

Example 89

N1-{4-[(9-fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
[d][1,3]thiazol-2-yl)amino]benzyl}-2-methoxyacetamide: To
5 a stirred solution of N2-[4-(aminomethyl)phenyl]-9-fluoro-
5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine
(See example 90) (1.50 g, 3.64 mmol) in anhydrous pyridine
(10 ml) and diisopropylethylamine (5.0 ml) was added
methoxyacetyl chloride (0.40 ml, 4.38 mmol) dropwise. The
10 solution was stirred overnight, poured into water (200 ml)
and extracted with EtOAc (200 ml). The extract was
evaporated to yield 1.8 g of a viscous golden oil. The
oil was chromatographed on silica-gel eluting with EtOAc
to yield 80% (1.2 g) of the desired product as a foam.
15 The product was converted to its HCl salt in chloroform
using 1M HCl in Et₂O: m.p. (HCl salt) 175-178 °C; ¹H-NMR
(CDCl₃) δ 2.15 (2H, m), 2.86 (4H, m), 3.42 (3H, s), 3.96
(2H, s), 4.50 (2H, d, J = 6.1 Hz), 7.00 (1H, t), 7.18-7.40
(7H, m), 7.61 (1H, dd, J = 2.5 Hz, 9.5 Hz); 412 (ESMS,
20 MH⁺).

Example 90

N-{4-[(9-Fluoro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta-
25 [d][1,3]thiazol-2-yl)amino]benzyl}methanesulfonamide:

N2-[4-(Aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4*H*-
benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine:
30 6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5*H*-
benzo[a]cyclohepten-5-one: To a stirred solution of 8-
fluoro-1-benzosuberone (20.00g, 112.2 mmol) in glacial
acetic acid (125 ml) was added bromine (5.8 ml, 112.6
mmol) dropwise. Once the addition was complete, the

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solution was poured into water (400 ml) and extracted with EtOAc (500 ml). The extract was separated and washed with water (500 ml). The organic layer was dried over MgSO_4 , filtered and evaporated to yield 100% (28.9 g) of the desired product as a viscous oil: ^1H -NMR (CDCl_3) δ 2.00 (2H, m), 2.33 (2H, m), 2.84 (1H, m), 3.00 (1H, m), 4.83 (1H, m), 7.13 (2H, m), 7.29 (1H, dd).

tert-Butyl N-(4-Aminobenzyl)carbamate: To a stirred solution of 4-amino-benzylamine (7.5 g, 61.39 mmol) in anhydrous THF (100 ml) under N_2 was added di-t-butyl dicarbonate (13.5 g, 61.9 mmol) in portions. The solution was stirred at room temperature under N_2 for 90 minutes. The solvent was removed in vacuo to yield 100% (13.7 g) of the Boc-protected amine as a white solid: m.p. 70-72 °C; ^1H -NMR (CDCl_3) δ 1.43 (9H, s), 3.62 (2H, broad), 4.18 (2H, d), 4.77 (1H, broad), 6.63 (2H, d), 7.06 (2H, d).

tert-Butyl N-(4-{[(Benzoylamino)carbothioyl]amino}benzyl)-carbamate: To a stirred solution of tert-butyl N-(4-aminobenzyl)carbamate (6.00 g, 27.0 mmol) in anhydrous THF (50 ml) was added benzoylisothiocyanate (4.43 g, 27.0 mmol). The solution was stirred for 2 hours and the solvent removed in vacuo to yield 100% (10.4 g) of the protected thiourea as a yellow solid: m.p. 161-163 °C; ^1H -NMR (CDCl_3) δ 1.45 (9H, s), 4.33 (2H, d), 4.85 (1H, broad), 7.34 (2H, d), 7.60 (5H, m), 7.90 (2H, d), 9.13 (1H, s), 12.58 (1H, s); 386 (ESMS, MH^+).

tert-Butyl N-{4-[(Aminocarbothioyl)amino]benzyl}-carbamate: To a stirred near solution of tert-butyl N-(4-{[(benzoylamino)carbothioyl]amino}benzyl)-carbamate (10.4 g, 27.0 mmol) in MeOH (150 ml) was added a solution of K_2CO_3 (8.5 g, 61.5 mmol) in 15 ml water. The solution was

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stirred at room temperature for 24 hours and filtered to remove a white precipitate. The filtrate was evaporated in vacuo to yield 100% (7.6 g) of the desired product as an off-white solid.

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tert-Butyl N-{4-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-yl)amino]benzyl}-carbamate: A solution containing tert-butyl N-{4-[(aminocarbothioyl)-amino]benzyl}carbamate (7.60 g, 27.0 mmol), 6-bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (6.95 g, 27.0 mmol) and diisopropylethylamine (5.0 ml) in EtOH (60 ml) was heated at reflux for 2.5 hours. The solvent was removed in vacuo and the residue dissolved in EtOAc (125 ml). The resulting solution was filtered to remove the insoluble (i-pr)₂NEt•HBr. The filtrate was transferred to a 250 ml round bottom flask and 4N HCl in dioxane (35 ml) was added with stirring. The solution was stirred for 90 minutes and then filtered to collect the hydrochloride salt. The solid was washed with EtOAc and then with Et₂O. Upon drying, 86% (11.1 g) of the Boc-protected amine hydrochloride was obtained as a pale yellow solid: ¹H-NMR (d₄-MeOH) δ 1.43 (9H, s), 2.18 (2H, m), 2.80 (4H, m), 4.25 (2H, s), 7.12 (1H, dt), 7.33 (2H, m), 7.43 (4H, s).

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N2-[4-(aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: To a stirred near solution of tert-butyl [4-(4H-chromeno[4,3-d][1,3]thiazol-2-ylamino)cyclohexyl]-methylcarbamate (11.1 g, 23.3 mmol) in MeOH (150 ml) was added 4N HCl in dioxane (40 ml). The solution was brought to a brief gentle reflux and the solvent then removed in vacuo. The resulting solid was re-suspended in Et₂O, filtered and dried to yield 90% (9.25 g) of the desired di-

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hydrochloride salt as a white solid: m.p. 236-239 °C; ¹H-NMR (CDCl₃) δ 1.75 (2H, broad), 2.06 (2H, m), 2.77 (2H, m), 2.83 (2H, t), 3.79 (2H, s), 6.82 (1H, t), 7.04 (1H, m), 7.22 (4H, m), 7.79 (1H, dd), 8.8 (1H, broad); 340 (ESMS, MH⁺).

To a stirred solution of N2-[4-(aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-amine (1.50 g, 3.64 mmol) in anhydrous pyridine (10 ml) and diisopropylethylamine (5.0 ml) was added methanesulfonyl chloride (0.38 ml, 4.91 mmol) dropwise. The solution was stirred at room temperature overnight, poured into water (250 ml) and extracted with EtOAc. The extract was evaporated to yield 1.7 g of the crude product as a viscous orange oil. The oil was chromatographed on silica-gel eluting with EtOAc (R_f of product ~ 0.9) to yield 66% (1.0 g) of the desired product as a solid. The solid was triturated with Et₂O/hexane (1:1) and filtered to give 0.93 g of the product as a pale yellow solid: m.p. 148-150 °C; ¹H-NMR (CDCl₃) δ 2.13 (2H, m), 2.79 (2H, m), 2.89 (3H, s), 2.91 (2H, m), 4.24 (2H, d, J = 4.3 Hz), 5.06 (1H, m), 6.88 (1H, t), 7.13 (1H, t), 7.30 (4H, m), 7.48 (1H, m), 7.72 (1H, dd, J = 2.7 Hz, 10.6 Hz); 418 (ESMS, MH⁺).

I. Synthetic Methods for ExamplesB. Bicyclic Compounds5 **General Procedures Relating to Examples:**

For the formation of 2-aminothiazoles from 2-haloketones and thioureas, see, for example, Kearney, P.C., et al., 1998; Di Fabio, R. and Pentassuglia, G., 1998; De Kimpe, N., et al., 1996; Plazzi, P.V., et al., 1995; and
10 Novikova, A. P., 1991.

For the formation of thiazoles from 2-haloketones and thioamides, see, for example, Critcher, D. J. and Pattenden, G., 1996; and Friedman, B. S., et al., 1937.

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For the formation of 2-aminoimidazoles from 2-haloketones and guanidines, see, for example, Little, T. L. and Webber, 1994; and Chabaka, L.M., et al., 1994.

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For the formation of imidazoles from 2-haloketones and amidines, see, for example, Demchenko, A. M., et al., 1997; and Nagao, Y., et al., 1996.

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For the synthesis of 2-aminooxazoles from 2-haloketones and ureas, see, for example, Pathak, V.N., et al., 1993; Crangk, G. and Foulis, M.J., 1971; and Marchetti, E., et al., 1968.

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For the formation of oxazoles from 2-haloketones and amides, see, for example, Hammar, W.J. and Rustad, M.A., 1981; and Zhao, Z., et al., 1991.

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Benzotriazole-1-carboxaldehyde was purchased from Aldrich Chemical Company and is recommended for the formation of formamides from amines.

5 All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. The
10 examples 1-9 described in the application were named using ACD/Name program (version 2.51, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

¹H and ¹³C spectra were recorded at 300 and 75 MHz (QE
15 Plus) with CDCl₃ as solvent (unless otherwise noted) and tetramethylsilane as internal standard. s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sextet; septet; b = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Low-
20 resolution electrospray MS spectra were measured (ESMS, MS) and MH⁺ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-
25 layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). Melting points were determined in open capillary tubes on a Med-Temp apparatus and are uncorrected.

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General Procedure for the Synthesis of Bromoketones:

To a cooled solution of the ketone (1 equivalent) in acetic acid or an appropriate solvent, cooled in a water bath, was slowly added bromine or a brominating agent such as tetrabutylammonium perbromide (1 equivalent). The reaction mixture was stirred at room temperature. The solvent was evaporated and the residue was dissolved in dichloromethane, and washed with saturated sodium bicarbonate and water. The organic phase was dried over sodium sulfate. Evaporation of the combined decolorized organic phase afforded a light yellow oil. In some cases, the desired product precipitated upon concentration of the reaction mixture. Many of the bromoketones used in this application were commercially available.

General Procedure for the Synthesis of Thioureas:

A protected diamine such as N-Boc-1,4-diaminobutane or N-Boc-1,5-diaminopentane (1 equivalent) was dissolved in tetrahydrofuran and stirred at room temperature. Benzoyl isothiocyanate (1.1 equivalent) was added dropwise to the aforementioned solution. The resulting mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to give a yellow oil. The yellow oil (1 equivalent) was dissolved in methanol, an aqueous potassium carbonate (3 equivalents) solution was added, and the mixture stirred for 48 hours. Water was added to the reaction mixture and extracted with 2x75 ml ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give the desired thiourea.

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The following procedure is typical:

a. **t-Butyl-trans-N-(4-(benzoylaminocarbothioylamino)-cyclohexyl)methyl-carbamate:** A solution of t-butyl trans-N-(4-aminocyclohexyl)methylcarbamate (4.68 g, 20.5 mmol) and benzoylisothiocyanate (3.77 g, 23.1 mmol) in THF (180 ml) was stirred at room temperature for 20 hours. The solvent was removed in vacuo to yield a golden viscous oil. The oil was triturated with hexanes (250 ml). The resulting solid was collected by filtration and washed with hexanes to yield 91% (7.32 g) of the product as an off-white solid: ^1H NMR (CDCl_3) δ 1.20 (6H, m), 1.44 (9H, s), 1.83 (2H, m), 2.25 (2H, m), 3.01 (2H, t, $J = 6.4$ Hz), 4.20 (1H, m), 4.62 (1H, m), 7.51 (2H, t, $J = 7.9$ Hz), 7.60 (1H, t, $J = 7.4$ Hz), 7.81 (2H, d, $J = 7.2$ Hz), 8.93 (1H, s); ESMS $m/e = 392$ (MH^+).

b. **t-Butyl trans-N-(4-(aminocarbothioylamino)-cyclohexyl)-methylcarbamate:** To a solution of t-butyl trans-N-(4-(benzoylaminocarbothioylamino)-cyclohexyl)methyl-carbamate (7.30 g, 18.6 mmol) in MeOH (110 ml) was added an aqueous solution of potassium carbonate (5.15 g, 37.3 mmol in 50 ml). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed in vacuo and the residue was extracted several times with EtOH. The combined EtOH extracts were evaporated to dryness to yield 6.15 g of an off-white solid. The solid was dissolved in acetone (200 ml) and stirred for 20 minutes. The solution was filtered by suction to remove any insoluble salts and the filtrate was evaporated to yield 98% (5.23 g) of the desired product as a slightly yellow solid: ^1H NMR (CDCl_3) δ 1.10 (6H, m), 1.43 (9H, s), 1.80 (2H, m), 2.10 (2H, m), 2.95 (2H, t, $J =$

6.4 Hz), 4.75 (1H, broad), ¹⁶⁰6.03 (2H, s), 6.64 (1H, broad); ESMS m/e = 288 (MH⁺).

5 *tert*-Butyl 5-[(aminocarbothioyl)amino]pentylcarbamate was obtained as a light yellow wax from *tert*-butyl 5-{[(benzoylamino)carbothioyl]amino}-pentylcarbamate: ¹H NMR (CD₃OD) δ 3.44 (m, 1H), 3.10 (m, 1H), 3.01 (t, 2H, *J* = 6.7 Hz), 1.60-1.31 (m, 6H), 1.41 (s, 9H); 262 (ESMS, MH⁺).

10 *tert*-Butyl-5-{[(benzoylamino)carbothioyl]amino}-pentylcarbamate was obtained as a light yellow solid in 79% yield from *N*-BOC-1,5-diaminopentane and benzoyl isothiocyanate: m.p. 90-93 °C.

15 *trans-tert*-Butyl-{4-[(aminocarbothioyl)amino]-cyclohexyl}methylcarbamate was obtained as a light yellow wax from *trans-tert*-butyl-(4-{[(benzoylamino)carbothioyl]amino}-cyclohexyl)-methylcarbamate: ¹H NMR (CD₃OD) δ 3.92 (m, 1H), 2.86 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.37 (m, 1H), 1.06 (m, 4H); 288 (ESMS, MH⁺).

25 *trans-tert*-Butyl-(4-{[(benzoylamino)carbothioyl]amino}cyclohexyl)methylcarbamate was obtained as a yellow solid in 97% yield from *tert*-butyl 4-aminocyclohexylmethylcarbamate and benzoyl isothiocyanate.

30 *trans-tert*-Butyl 4-aminocyclohexylmethylcarbamate was obtained in more than 95% yield by hydrogenation of benzyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-cyclocarbamate.

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Benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate: To a stirred suspension of 4-[[[(tert-butoxycarbonyl)amino]methyl]cyclohexanecarboxylic acid (Maybridge Chemical Co., Ltd.) (45g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) was added triethylamine (32 ml) over a period of 20 min whilst maintaining the internal temperature at -10-0 C. The mixture was slowly warmed and then stirred at 70 C for 4h. After cooling to 40 C, benzyl alcohol (36 ml) was added and the reaction mixture heated at reflux for 20 h. The cold reaction mixture was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallization of the organic residue from ethyl acetate and diethyl ether gave the title compound, benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate as a white solid, m.p. 129-131 C.

trans-Benzyl-4-{[(aminocarbothioyl)amino]methyl}-cyclohexyl-carbamate was obtained as a yellow solid in 71% yield from trans-benzyl 4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate: 322 (ESMS, MH⁺).

trans-Benzyl-4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate was obtained as a yellow solid from benzyl 4-(aminomethyl)cyclohexylcarbamate and benzoyl isothiocyanate.

trans-Benzyl 4-(aminomethyl)cyclohexylcarbamate was obtained as a white solid in more than 95% yield by stirring benzyl 4-{[(tert-butoxycarbonyl)amino]-methyl}-

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cyclocarbamate in 2N HCl (made from 1 : 1 of EtOAc and 4N HCl in dioxane).

General Procedure for the Synthesis of Bicyclic Thiazoles:

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A mixture of a bromoketone (1 equivalent), thiourea (1 equivalent), and diisopropylethylamine (2 equivalents) in acetone or anhydrous ethanol was heated at reflux temperature overnight. The solvent was evaporated, the residue dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane three times, the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes : ethyl acetate).

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The following procedure is typical:

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c. trans-2-(4-(t-Butoxycarbonylaminomethyl)-cyclohexyl)-amino-4-(2-methoxy-phenyl)1,3-thiazole: A mixture of 2-bromoacetylanisole (1.5 g, 6.5 mmol), trans-4-(aminocarbothioylamino)-1-(t-butoxycarbonyl-amino)methyl-cyclohexane (1.88 g, 6.5 mmol) and N,N-diisopropylethylamine (2.3 ml, 13.1 mmol) in acetone (20 ml) was heated at reflux temperature overnight. The solvent was evaporated, the residue was dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography over silica gel (hexanes/ethyl acetate 5:2) to give the desired product as a light brown oil (1.2 g, 44% yield): ESMS m/e = 418 (MH⁺): ¹H NMR δ 8.08 (dd, 1H, J

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= 1.6, 7.7 Hz), 7.24 (m, 1H), 7.18 (s, 1H), 7.01 (t, 1H, $J = 7.6$ Hz), 6.95 (d, 1H, $J = 8.2$ Hz), 4.96 (d, 1H, $J = 8.1$ Hz), 4.60 (m, 1H), 3.93 (s, 3H), 3.30 (m, 1H), 3.01 (t, 2H, $J = 6.4$ Hz), 2.25 (m, 2H), 1.84 (m, 2H), 1.47 (m, 1H), 1.45 (s, 9H), 1.30-1.03 (m, 4H).

tert-Butyl-(4-{[4-(2-methoxyphenyl)-1,3-thiazol-2-yl]amino}cyclohexyl)methylcarbamate was obtained as a light brown oil in 95% yield from 2-bromo-2'-methoxyacetophenone and tert-butyl {4-[(aminocarbothioyl)amino]cyclohexyl}-methylcarbamate: ^1H NMR δ 8.08 (dd, 1H, $J = 1.6, 7.7$ Hz), 7.24 (m, 1H), 7.18 (s, 1H), 7.01 (t, 1H, $J = 7.6$ Hz), 6.95 (d, 1H, $J = 8.2$ Hz), 4.96 (d, 1H, $J = 8.1$ Hz), 4.60 (m, 1H), 3.93 (s, 3H), 3.30 (m, 1H), 3.01 (t, 2H, $J = 6.4$ Hz), 2.25 (m, 2H), 1.84 (m, 2H), 1.47 (m, 1H), 1.45 (s, 9H), 1.30-1.03 (m, 4H); ESIMS $m/e = 418$ (MH^+).

tert-Butyl-(4-{[4-(3-methoxyphenyl)-1,3-thiazol-2-yl]amino}cyclohexyl)methylcarbamate was obtained as a yellow oil in 86% yield from 2-bromo-3'-methoxyacetophenone and tert-butyl {4-[(aminocarbothioyl)amino]cyclohexyl}-methylcarbamate: ^1H NMR δ 7.36 (m, 2H), 7.30 (m, 1H), 6.83 (m, 1H), 6.68 (s, 1H), 5.05 (d, 1H, $J = 7.9$ Hz), 4.60 (m, 1H), 3.85 (s, 3H), 3.29 (m, 1H), 3.01 (t, 2H, $J = 6.4$ Hz), 2.26 (m, 2H), 1.86 (m, 2H), 1.46 (m, 1H), 1.45 (s, 9H), 1.30-1.03 (m, 4H); ESIMS $m/e = 418$ (MH^+).

tert-Butyl-(4-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}cyclohexyl)methylcarbamate was obtained as a yellow oil in 86% yield from 2-bromo-4'-methoxyacetophenone and tert-butyl-{4-[(aminocarbothioyl)amino]cyclohexyl}-methylcarbamate: ^1H NMR δ 7.71 (d, 2H, $J = 8.4$ Hz), 6.90 (d, 2H,

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$J = 8.4$ Hz), 6.55 (s, 1H), 5.01 (m, 1H), 4.60 (m, 1H), 3.83 (s, 3H), 3.29 (m, 1H), 3.01 (t, 2H, $J = 6.3$ Hz), 2.25 (m, 2H), 1.86 (m, 2H), 1.46 (m, 1H), 1.45 (s, 9H), 1.28-1.02 (m, 4H); ESIMS $m/e = 418$ (MH^+).

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tert-Butyl-[4-({4-[4-(aminocarbonyl)phenyl]-1,3-thiazol-2-yl}amino)cyclohexyl]methylcarbamate was obtained as a yellow solid in more than 95% yield from 4-(2-bromoacetyl)benzamide (1 equivalent) and tert-butyl-{4-
10 [(aminocarbothioyl)amino]cyclohexyl}-methylcarbamate (1 equivalent, no diisopropylethylamine was added for this reaction): 1H NMR (CD_3OD) δ 7.94 (d, 2H, $J = 8.4$ Hz), 7.79 (d, 2H, $J = 8.4$ Hz), 7.07 (s, 1H), 3.57 (m, 1H), 2.91 (d, 2H, $J = 6.6$ Hz), 2.17 (m, 2H), 1.86 (m, 2H), 1.42 (s, 9H),
15 1.39 (m, 3H), 1.10 (m, 2H); ESIMS $m/e = 431$ (MH^+).

General Procedure for the Deprotection of the Boc-bicyclic Thiazoles Intermediates.

20 The Boc-protected 2-amino-1,3-thiazole intermediate was treated with 2N hydrogen chloride in 1,4-dioxane and ethyl acetate (prepared from 4N HCl in dioxane) at room temperature for 2 hours or longer as needed. The desired compound was collected by filtration.

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N-[4-(Aminomethyl)cyclohexyl]-4-(2-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride was obtained as a light yellow solid in more than 95% yield from tert-butyl-(4-{[4-(2-methoxyphenyl)-1,3-thiazol-2-yl]amino}-
30 cyclohexyl)methyl-carbamate: 1H NMR (CD_3OD) δ 7.54-7.45 (m, 2H), 7.16 (d, 1H, $J = 8.4$ Hz), 7.06 (m, 1H), 7.01 (s, 1H), 3.92 (s, 3H), 3.63 (d, 2H, $J = 1.2$ Hz), 3.50 (m, 1H), 2.83 (m, 2H), 2.21 (m, 2H), 1.96 (m, 2H), 1.69 (m, 1H), 1.49 (m, 2H), 1.22 (m, 2H); ESI $m/e = 318$ (MH^+).

N-[4-(Aminomethyl)cyclohexyl]-4-(3-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride was obtained as a pale solid in more than 95% yield from *tert*-butyl (4-{[4-(3-methoxyphenyl)-1,3-thiazol-2-yl]-amino}cyclohexyl)methyl-carbamate.

N-[4-(Aminomethyl)cyclohexyl]-4-(4-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride was obtained as a pale solid in more than 95% yield from *tert*-butyl-(4-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-amino}cyclohexyl)methyl-carbamate: ¹H NMR (CD₃OD) δ 7.60 (d, 2H, *J* = 8.6 Hz), 7.02 (d, 2H, *J* = 8.6 Hz), 6.89 (s, 1H), 3.83 (s, 3H), 3.63 (m, 1H), 2.85 (m, 2H), 2.20 (m, 2H), 1.95 (m, 2H), 1.72 (m, 1H), 1.52 (m, 2H), 1.28 (m, 2H).

trans-4-(2-{[4-(Aminomethyl)cyclohexyl]amino}-1,3-thiazol-4-yl)benzamide dihydrogen chloride was obtained as a yellow solid in more than 95% yield from *tert*-butyl [4-({4-[4-(aminocarbonyl)phenyl]-1,3-thiazol-2-yl}amino)cyclohexyl]-methylcarbamate: ¹H NMR (CD₃OD) δ 7.99 (d, 2H, *J* = 8.5 Hz), 7.78 (d, 2H, *J* = 8.5 Hz), 7.19 (s, 1H), 3.69 (m, 1H), 2.84 (m, 1H), 2.21 (m, 2H), 1.95 (m, 2H), 1.71 (m, 1H), 1.53 (m, 2H), 1.08 (m, 2H).

General Procedure for the Derivatization of Amines with Carboxylic Acid and Sulfonic Acid Derivatives:

An amine such as N1 -(4,5-Dihydrobenzo[2,3]thiepino-[4,5-d][1,3]thiazol-2-yl)-1,6-hexanediamine or N2-[4-(aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]-thiepino[4,5-d][1,3]thiazol-2-amine (0.305 mmol) was dissolved in 2 ml CH₂Cl₂ containing 2 equivalents of diisopropylethylamine. A sulfonyl chloride, sulfamoyl

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chloride, acid chloride or carbamoyl chloride (1-3 equivalents) was added dropwise. The reaction mixture was stirred at room temperature for 1-3 days, quenched with water, washed with 10% NaHCO₃, dried over Na₂SO₄ and chromatographed using column chromatography, preparative TLC or reverse phase HPLC.

10

General Procedure for the Formation of Formamides:

tert-Butyl-*N*-[4-(isopropylamino)cyclohexyl]methylcarbamate:

15 Isopropyl iodide (2 equivalents) was added dropwise to a suspension of *tert*-butyl *N*-[4-aminocyclohexyl]methylcarbamate (1 equivalent) and diisopropylethyl amine (3 equivalents) in THF. The resulting mixture was stirred for 1 day. TLC analysis showed some starting amine.

20 Additional isopropyl iodide (1 equivalent) and diisopropylethyl amine (3 equivalents) were added to the reaction mixture and heated at 40 °C for 1 day. The reaction mixture was concentrated and chromatographed to give *tert*-butyl *N*-[4-(isopropylamino)cyclohexyl]methylcarbamate: 22% yield, 271 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 4.65 (broad, 1H), 2.91 (m, 3H), 2.42 (m, 1H), 1.80 (ABm, 4H), 1.38 (s, 9H), 0.98 (d, 6H, J=6.3 Hz), 1.32-0.85 (m, 5H).

30 Similarly, *tert*-butyl-*N*-[4-(2-methoxyethylamino)cyclohexyl]methylcarbamate was obtained (2-methoxyethyl bromide and n-Bu₄NI were used): 35% yield, 378 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 4.64 (broad, 1H), 3.44 (m, 2H), 3.31 & 3.30 (two s, 3H), 2.92 (m, 2H), 2.74 (m, 2H), 2.33 (m,

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1H), 1.81 (ABm, 4H), 1.39 & 1.38 (two s, 9H), 1.34 (m, 1H), 0.98 (m, 4H).

5 *tert*-butyl *N*-[4-(isopropylformylamino)cyclohexyl]-methylcarbamate: A solution of a *tert*-butyl *N*-[4-(isopropylamino)cyclohexyl]methylcarbamate (7.89 mmol, 1 equivalent) in 5 ml of THF was added dropwise to a solution of 1H-benzotriazole-1-carboxaldehyde (8.68 mmol, 1.2 equivalent) in 10 ml of THF at room temperature. The
10 reaction mixture was stirred overnight and then heated at reflux temperature for two hours. 1H-benzotriazole-1-carboxaldehyde (additional 1 equivalent) was added to the reaction mixture and stirred overnight. The solvent was removed in vacuo and dichloromethane was added to the
15 residue. The organic phase was washed with 2N NaOH solution, saturated NaCl solution, dried over Na₂SO₄, and the solvent removed in vacuo. The residue was then chromatographed to give *tert*-butyl *N*-[4-(isopropylformylamino)cyclohexyl]methylcarbamate: 100%
20 yield, 299 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.22 & 8.18 (two s, 1H), 4.63 (broad, 1H), 4.30 & 3.60 (two m, 1H), 3.76 (m, 1H), 2.99 (m, 2H), 1.44 (s, 9H), 1.27 (d, 3H, J=6.5 Hz), 1.21 (d, 3H, J=6.5 Hz), 1.91-0.82 (m, 9H).

25 Similarly, *N*-[4-(2-methoxyethylformylamino)-cyclohexyl]-methylcarbamate was prepared: 58% yield; 315 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.25 & 8.16 (two s, 1H), 4.80 (broad, 1H), 4.07 & 3.23 (two m, 1H), 3.50 (m, 2H), 3.40-3.33 (m, 2H), 3.31 (s, 3H), 2.99 (m, 2H), 1.46 (s, 9H),
30 1.86-0.95 (m, 9H).

***N*-[4-(Aminomethyl)cyclohexyl]-*N*-isopropylformamide:**

Dioxane containing HCl (10 ml of 4N HCl solution) was added to a solution of *tert*-butyl *N*-[4-

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(isopropylformylamino)-cyclohexyl)methylcarbamate dissolved in 10 ml Et₂O, stirred at room temperature for 2 hours, and the solvent removed to obtain N-[4-(aminomethyl)cyclohexyl]-N-isopropylformamide: 100% yield, 199 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.16 (s, 1H), 4.16 & 3.57 (two m, 1H), 3.70 (m, 1H), 2.79 (m, 2H), 1.36 (m, 6H), 1.91-1.06 (m, 9H).

Similarly, N-[4-(aminomethyl)cyclohexyl]-N-(2-methoxyethyl)-formamide was obtained: 100% yield; 215 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.44 & 8.03 4.65 (two s, 1H), 3.79-3.36 (m, 7H), 3.71 (s, 3H), 2.12-1.13 (m, 9H).

N-Benzoyl-N'-[4-(isopropylformylamino)cyclohexyl]-methylthiourea: A mixture of N-[4-(aminomethyl)-cyclohexyl]-N-isopropylformamide salt (4.55 mmol, 1 equivalent), benzoyl isothiocyanate (5.46 mmol, 1.2 equivalents) and triethylamine (5.46 mmol, 1.2 equivalents) in THF (50 ml) were stirred at room temperature overnight. The removal of solvent and chromatography afforded the desired product: 39% yield, 362 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 10.87 (broad, 1H), 9.20 (broad, 1H), 8.20 & 8.18 (two s, 1H), 7.83 (d, 2H, J=7.7 Hz), 7.60 (m, 1H), 7.49 (m, 2H), 4.26 (m, 1H), 3.76 & 3.08 (two m, 1H), 3.57 (m, 2H), 1.25 (d, 3H, J=6.8 Hz), 1.19 (d, 3H, J=6.8 Hz), 1.97-1.03 (m, 9H).

Similarly, N-Benzoyl-N'-[4-(2-methoxyethylformyl-amino)-cyclohexyl)methylthiourea was obtained: 100% yield, 378 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 10.85 (broad, 1H), 9.03 (broad, 1H), 8.18 & 8.08 (two s, 1H), 7.84 (d, 2H, J=7.9 Hz), 7.64 (m, 1H), 7.52 (d, 2H, J=7.8 Hz), 3.63-3.24 (m, 7H), 3.34 & 3.33 (two m, 3H), 2.03-1.13 (m, 9H).

N-[4-

(isopropylformylamino)cyclohexyl]methylthiourea: K_2CO_3 (2 equivalents) in water was added to a solution of *N*-benzoyl-*N'*-[4-(isopropylformylamino)-cyclohexyl]methyl-
5 thiourea in MeOH and stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in EtOH. The solution was filtered to remove a white precipitate and the filtrate concentrated. The crude product was chromatographed to
10 yield the desired product: 100% yield; 100% yield; 258 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.15 & 8.13 (two s, 1H), 4.15 & 3.73 (two m, 1H), 3.34 & 2.97 (two m, 1H), 3.29 (m, 2H), 1.26 (d, 3H, $J=6.7$ Hz), 1.23 (d, 3H, $J=6.7$ Hz), 1.91-1.03 (m, 9H).

15

Similarly, *N*-[4-(2-methoxyethylformylamino)-cyclohexyl]-methylthiourea was prepared: 77% yield, 274 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.15 & 8.00 (two s, 1H), 7.55 & 7.43 (two m, 1H), 3.90 & 2.97 (two m, 1H), 3.46-3.28 (m, 10H), 1.90-
20 0.99 (m, 9H).

Formation of 2-amino-1,3-thiazoles containing a formamide:

A thiourea such as *N*-[4-(isopropylformylamino)cyclohexyl]-methylthiourea (0.029 mmol, 1 equivalent), a bromoketone
25 such as 2-bromoacetylbenzene (0.044 mmol, 1.5 equivalents) and 2 equivalents of diisopropylethyl amine in 10 ml of EtOH were heated at reflux temperature for 2 days. The reaction mixture was concentrated and the crude product
30 was chromatographed (silica) to afford the desired product. This sequence of reactions were utilized for the preparation of examples 98-99.

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Alternatively, the terminal amino functionality of a primary amine such as *N*-[4-(aminomethyl)cyclohexyl]-4-(2-methoxyphenyl)-1,3-thiazol-2-amine was alkylated using alkyl halides or a sequence of acylation followed by reduction to give a secondary amine. The secondary amine was, in turn, used in the formation of the formamide utilizing a formylating reagent such as benzotriazole-1-carboxaldehyde. This sequence of reactions were utilized in the preparation of examples 96-97.

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N-{4-[(isopropylamino)methyl]cyclohexyl}-4-(2-methoxyphenyl)-1,3-thiazol-2-amine: The reaction mixture of *N*-[4-(aminomethyl)cyclohexyl]-4-(2-methoxyphenyl)-1,3-thiazol-2-amine (1 equivalent), 2-iodopropane (1 equivalent), and potassium carbonate (2 equivalents) in DMF was heated at about 50 °C overnight. Water was then added to the reaction mixture and extracted with diethyl ether (3 times). Evaporation of the combined organic phase afforded a yellow oil which was purified by preparative TLC plates. The desired product was obtained as a yellow oil in 53% yield: ESIMS *m/e* = 360 (MH⁺).

15

N-(4-{[2-Methoxyethyl]amino}methyl)cyclohexyl)-4-(2-methoxyphenyl)-1,3-thiazol-2-amine was obtained as a light yellow oil in 82% yield from 2-methoxy-*N*-[(4-{[4-(2-methoxyphenyl)-1,3-thiazol-2-yl]amino}-cyclohexyl)methyl]-acetamide and borane (4 equivalents, 1M in THF): ESIMS *m/e* = 376 (MH⁺).

25

2-Methoxy-*N*-[(4-{[4-(2-methoxyphenyl)-1,3-thiazol-2-yl]amino}cyclohexyl)-methyl]acetamide was obtained as a yellow oil in 87% yield from *N*-[4-(aminomethyl)cyclohexyl]-4-(2-methoxyphenyl)-1,3-thiazol-2-amine and methoxyacetyl chloride.

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A sequence of reactions depicted in schemes 7-11 were utilized for the preparation of examples 91-95.

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Example 91

trans-4-(2-Methoxy)phenyl-2-(4-methylsulfonylamino-methyl)-cyclohexylamino-1,3-thiazole hydrochloride. Obtained as a white solid in 43% yield from *trans*-2-(4-aminomethyl)cyclohexylamino-4-(2-methoxyphenyl)-1,3-thiazole dihydrochloride and methanesulfonyl chloride: ESMS $m/e = 396$ (MH^+); 1H NMR (free base) δ 8.06 (dd, 1H, $J = 1.6, 7.7$ Hz), 7.25 (m, 1H), 7.17 (s, 1H), 7.03-6.94 (m, 2H), 5.09 (d, 1H, $J = 7.7$ Hz), 4.59 (m, 1H), 3.92 (s, 3H), 3.31 (m, 1H), 2.99 (t, 2H, $J = 6.5$ Hz), 2.96 (s, 3H), 2.26 (m, 2H), 1.88 (m, 2H), 1.49 (m, 1H), 1.29-1.07 (m, 4H).

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Example 92

trans-2-(4-Ethoxycarbonylaminomethyl)cyclohexylamino-4-(2-methoxy)phenylthiazole hydrogen chloride was obtained as a light yellow solid in 62% from *N*-[4-(aminomethyl)cyclohexyl]-4-(2-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride and ethyl chloroformate: 1H NMR ($CDCl_3$, free base) δ 8.07 (dd, 1H, $J = 1.3, 7.7$ Hz), 7.24 (m, 1H), 7.18 (s, 1H), 7.03-6.93 (m, 2H), 5.01 (m, 1H), 4.72 (m, 1H), 4.11 (q, 2H, $J = 7.0$ Hz), 3.93 (s, 3H), 3.31 (m, 1H), 3.06 (m, 2H), 2.26 (m, 2H), 1.85 (m, 2H), 1.49 (m, 1H), 1.24 (t, 3H, $J = 7.0$ Hz), 1.30-1.05 (m, 4H); ESIMS $m/e = 390$ (MH^+).

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Example 93

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trans-4-(3-Methoxy)phenyl-2-(4-methylsulfonylamino-methyl)-cyclohexylaminothiazole was obtained as a light yellow solid in 84% from *N*-[4-(aminomethyl)cyclohexyl]-4-(3-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride and methanesulfonyl chloride: ^1H NMR δ 7.36 (m, 2H), 7.27 (m, 1H), 6.83 (m, 1H), 6.69 (s, 1H), 5.08 (m, 1H), 4.33 (m, 1H), 3.85 (s, 3H), 3.35 (m, 1H), 3.02 (t, 2H, $J = 6.6$ Hz), 2.97 (s, 3H), 2.28 (m, 2H), 1.91 (m, 2H), 1.58 (m, 1H), 1.28-1.05 (m, 4H); ESIMS $m/e = 396$ (MH^+).

10

Example 94

trans-2-(4-Ethoxycarbonylaminomethyl)cyclohexylamino-4-(3-methoxy)phenylthiazole hydrogen chloride was obtained as a yellow solid in 81% from *N*-[4-(aminomethyl)cyclohexyl]-4-(3-methoxyphenyl)-1,3-thiazol-2-amine dihydrogen chloride and ethyl chloroformate: ^1H NMR (free base) δ 7.36 (m, 2H), 7.27 (m, 1H), 6.83 (m, 1H), 6.69 (s, 1H), 5.01 (m, 1H), 4.71 (m, 1H), 4.12 (m, 2H), 3.85 (s, 3H), 3.30 (m, 1H), 3.07 (t, 2H, $J = 6.5$ Hz), 2.25 (m, 2H), 1.86 (m, 2H), 1.49 (m, 1H), 1.30-1.08 (m, 7H); ESIMS $m/e = 390$ (MH^+).

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General Procedure for the Demethylation of Methoxyphenylthiazoles Using Boron Tribromide:

5 Boron tribromide (3 equivalents, 1M in CH₂Cl₂) was added dropwise to a cooled solution of methoxyphenylthiazole (1 equivalent) in dichloromethane. The reaction mixture was stirred at -78 °C for ten minutes, then warmed up to room temperature and stirred for an additional hour. Water was
10 added to destroy the boron complex and 2M sodium hydroxide was added to basify the mixture to pH 13-14. The resulting mixture was extracted with chloroform (3 times) and the combined organic extracts were dried and concentrated in vacuo. The crude product was purified by flash column
15 (silica gel, hexane : ethyl acetate). In most cases, a light yellow oil was obtained which was converted to a hydrogen chloride salt.

Example 95

trans-4-(2-Hydroxy)phenyl-2-(4-methylsulfonylamino-methyl)-cyclohexylaminothiazole was obtained as a light brown solid in 50% yield from trans-4-(2-methoxy)phenyl-2-(4-methylsulfonylaminomethyl)-cyclohexylaminothiazole hydrogen chloride and boron tribromide: ^1H NMR δ 11.01 (b, 1H), 8.10 (dd, 1H, $J = 1.4, 7.9$ Hz), 7.25 (m, 2H), 6.89 (m, 2H), 5.18 (d, 1H, $J = 7.5$ Hz), 4.46 (m, 1H), 3.39 (m, 1H), 3.00 (t, 2H, $J = 6.5$ Hz), 2.96 (s, 3H), 2.22 (m, 2H), 1.91 (m, 2H), 1.60 (m, 1H), 1.30-1.04 (m, 4H) ; ESIMS $m/e = 382$ (MH^+) .

Example 96

trans-2-(4-(N-Isopropyl)formamidomethyl)cyclohexyl-amino-4-(2-methoxy)phenylthiazole hydrogen chloride was obtained as a yellow solid in 70% from N-{4-[(isopropylamino)methyl]-cyclohexyl}-4-(2-methoxy-phenyl)-1,3-thiazol-2-amine and 1H-benzotriazole-1-carboxaldehyde: ^1H NMR (CDCl_3 , free base) δ 8.25 (s, 0.6 H), 8.08 (dd, 1H, $J = 1.7, 7.7$ Hz), 7.99 (s, 0.4H), 7.24 (m, 1H), 7.18 (s, 1H), 7.03-6.93 (m, 2H), 5.04 (t, 1H, $J = 8.7$ Hz), 4.31 (p, 0.4H, $J = 6.8$ Hz), 3.92 (s, 3H), 3.64 (p, 0.6H, $J = 6.8$ Hz), 3.31 (m, 1H), 3.11 (d, 1.3H, $J = 7.3$ Hz), 3.01 (d, 0.7 Hz, $J = 7.3$ Hz), 2.24 (m, 2H), 1.79 (m, 2H), 1.69 (m, 0.6H), 1.51 (m, 0.4H), 1.30-1.00 (m, 10H) ; ESIMS $m/e = 388$ (MH^+) .

Example 97

trans-2-(4-(*N*-(2-Methoxyethoxy)formamido)methyl)-cyclohexylamino-4-(2-methoxy)phenylthiazole hydrogen chloride was obtained as a yellow syrup in 70% from *N*-(4-{[2-methoxyethyl)amino]methyl}cyclohexyl)-4-(2-methoxyphenyl)-1,3-thiazol-2-amine and 1*H*-benzo-triazole-1-carboxaldehyde: ¹H NMR (CDCl₃, free base) δ 8.11 (s, 0.4H), 8.08 (dd, 1H, *J* = 1.6, 7.8 Hz), 8.02 (s, 0.6 H), 7.24 (m, 1H), 7.18 (s, 1H), 7.00 (t, 1H, *J* = 7.5 Hz), 6.94 (d, 1H, *J* = 8.2 Hz), 5.01 (m, 1H), 3.92 (s, 3H), 3.56-3.14 (m, 7H), 2.25 (m, 2H), 1.76 (m, 2H), 1.66 (m, 1H), 1.29-0.97 (m, 4H); ESIMS *m/e* = 404 (MH⁺).

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Example 98

trans-N-(2-Methoxyethyl)-*N*-(4-[(4-phenyl-1,3-thiazol-2-yl)amino]methylcyclohexyl)formamide: 29% yield, 374 (ESMS, MH⁺): ¹H NMR (CDCl₃) δ 8.18 & 8.08 (two s, 1H), δ 7.78 (d, 2H, *J*=8.6 Hz), 7.37 (apparent t, 2H, *J*=7.7 Hz), 7.29 (d, 1H, *J*=7.0 Hz), 6.69 (s, 1H), 5.49 (b, 1H), 4.09 (m, 1H), 3.49-3.13 (m, 7H), 3.34 & 3.33 (two s, 3H), 2.00-0.85 (m, 9H).

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Example 99

trans-N-Isopropyl-*N*-(4-[(4-phenyl-1,3-thiazol-2-yl)amino]methylcyclohexyl)formamide: 84% yield, 358 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.21 & 8.17 (two s, 1H), δ 7.78 (d, 2H, *J*=8.7 Hz), 7.37 (apparent t, 2H, *J*=7.7 Hz), 7.28 (d, 1H, *J*=7.0 Hz), 6.68 (s, 1H), 5.63 & 5.77 (two b, 1H), 4.28 & 3.58 (two m, 1H), 3.78 & 3.03 (two m, 1H), 3.14 (m, 2H), 1.27 (d, 3H, *J*=6.9 Hz), 1.21 (d, 3H, *J*=6.9 Hz), 1.96-1.03 (m, 9H).

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I. Synthetic Methods for ExamplesC. Tricyclic Compounds5 **General Procedures Relating to Examples:**

For the formation of 2-aminothiazoles from 2-haloketones and thioureas, see, for example, Kearney, P.C., et al., 1998; Di Fabio, R. and Pentassuglia, G., 1998; De Kimpe, N., et al., 1996; Plazzi, P.V., et al., 1995; and
10 Novikova, A. P., 1991.

For the formation of thiazoles from 2-haloketones and thioamides, see, for example, Critcher, D. J. and Pattenden, G., 1996; and Friedman, B. S., et al., 1937.

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For the formation of 2-aminoimidazoles from 2-haloketones and guanidines, see, for example, Little, T. L. and Webber, 1994; and Chabaka, L.M., et al., 1994.

20 For the formation of imidazoles from 2-haloketones and amidines, see, for example, Demchenko, A. M., et al., 1997; and Nagao, Y., et al., 1996.

For the synthesis of 2-aminooxazoles from 2-haloketones and ureas, see, for example, Pathak, V.N., et al., 1993; Crangk, G. and Foulis, M.J., 1971; and Marchetti, E., et
25 al., 1968.

For the formation of oxazoles from 2-haloketones and amides, see, for example, Hammar, W.J. and Rustad, M.A.,
30 1981; and Zhao, Z., et al., 1991.

All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents,

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were transferred to the reaction vessel via syringe and cannula techniques. The parallel synthesis reaction arrays were performed in vials (without an inert atmosphere) using J-KEM heating shakers (Saint Louis, MO).
5 Unless stated otherwise all solvents were AR grade and used as supplied. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. Examples 1-7 described in this application were named using ACD/Name program (version 2.51, Advanced Chemistry Development
10 Inc., Toronto, Ontario, M5H2L3, Canada).

^1H and ^{13}C spectra were recorded at 300 and 75 MHz (QE Plus) with CDCl_3 as solvent (unless otherwise noted) and tetramethylsilane as internal standard. s = singlet; d =
15 doublet; t = triplet; q = quartet; p = pentet; sextet; septet; b = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Low-resolution electrospray MS spectra were measured (ESMS, MS) and MH^+ is reported. Thin-layer chromatography (TLC)
20 was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60
25 (230 - 400 mesh). Melting points were determined in open capillary tubes on a Med-Temp apparatus and are uncorrected.

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General Procedure for the Synthesis of Benzothiepin-5-ones:

2,3,4,5-Tetrahydro-1-benzothiepin-5-one

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Step 1.

4-(phenylsulfanyl)butanoic acid:

10 Sodium methoxide (1.2 equivalent) was added to 60 ml of ethanol, in one portion, and the suspension was stirred at room temperature. Thiophenol (1 equivalent) was added to the above suspension and stirred at room temperature for an additional 30 minutes. Butyrolactone (1.1 equivalent) was then added and the resulting mixture was stirred at
15 reflux temperature for 6 hours, cooled to room temperature and concentrated in vacuo. The residual solid was washed with 200 ml hexane/ether 2:1, v/v. The solid was suspended in ice cold 2N HCl and stirred for 15 minutes. The solid was then filtered, washed with 100 ml hexane/ether and
20 dried under reduced pressure at room temperature to give 4-(phenylsulfanyl)butanoic acid as a tan solid: 52% yield; ^1H NMR (CDCl_3) δ 7.32-7.12 (m, 5H), 2.94 (t, 2H, $J=7.2$ Hz), 2.41 (t, 2H, $J=7.2$ Hz), 1.85 (p, 2H, $J=7.2$ Hz); Anal. Calc. For $\text{C}_{10}\text{H}_{12}\text{S}_1\text{O}_2$: C, 61.22; H, 6.12. Found: C, 61.16; H,
25 6.28.

A similar procedure was used for the synthesis of 4-(4-fluorophenylsulfanyl)butanoic acid: 60% yield; ^1H NMR (CDCl_3) δ 7.34 (m, 2H, 7.00 (m, 2H), 2.94 (t, 2H, $J=7.2$ Hz), 2.51 (t, 2H, $J=7.2$ Hz), 1.93 (p, 2H, $J=7.2$ Hz); Anal. Calc. For $\text{C}_{10}\text{H}_{11}\text{F}_1\text{S}_1\text{O}_2$: C, 56.07; H, 5.14. Found: C, 55.80; H, 5.19.

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Step 2.

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Benzothiepin-5-ones:

Polyphosphoric acid (6 equivalents) was heated to 80°C under argon. 4-(Phenylsulfanyl)butanoic acid, (1 equivalent) was added in portions and the mixture heated at 100°C for 2 hours. The reaction mixture was cooled, poured into ice cold water and then extracted with 2X100 ml ethyl acetate. The combined ethyl acetate extracts were washed with 100 ml water, 100 ml saturated sodium bicarbonate, and 100 ml water. The ethyl acetate extract was dried (anhydrous sodium sulfate), filtered and the solvent removed in vacuo to give a tan solid. This solid was dried to give 2,3,4,5-tetrahydro-1-benzothiepin-5-one: 52% yield; ¹H NMR (CDCl₃) δ 7.824 (dd, 1H, J=0.9, 7.5 Hz), 7.45 (dd, 1H, J=0.6, 6.9 Hz), 7.34-7.21 (m, 2H), 3.05 (t, 2H, J=6.6 Hz), 2.97 (t, 2H, J=6.6 Hz), 2.29 (p, 2H, J=6.6 Hz).

The above described procedure was also used to afford 7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one: 60% yield; ¹H NMR (CDCl₃) δ 7.51 (dd, 1H, J=3.0, 9.3 Hz), 7.41 (dd, 1H, J=8.7, 5.1 Hz), 7.04 (apparent dt, 1H, J=3.0, 4.8 Hz), 3.06 (t, 2H, J=6.6 Hz), 2.96 (t, 2H, J=6.6 Hz), 2.64 (t, 2H, J=6.9 Hz); Anal. Calc. For C₁₀H₁₀S₁O₁: C, 67.41; H, 5.61. Found: C, 67.48; H, 5.68.

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General Procedure for the Synthesis of Bromoketones:

To a cooled solution of the ketone (1 equivalent) in acetic acid, was slowly added bromine (1 equivalent). The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated, the residue dissolved in dichloromethane, and the resulting solution washed with saturated sodium bicarbonate and water. The organic phase was dried over sodium sulfate. Evaporation of the combined, decolorized organic phase gave a light yellow oil in > 80% yield in most cases.

7-Fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one was brominated according to the procedure described below to give 4-bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one. A similar procedure was also used to brominate 2,3,4,5-tetrahydro-1-benzothiepin-5-one.

4-Bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one:
7-Fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one (1 equivalent) was also dissolved in glacial acetic acid and stirring continued at room temperature. Bromine (2.5 equivalents) was added dropwise and stirring continued at room temperature for 4 hours. Water was added to the reaction mixture was then extracted with 2x25 ml ethyl acetate. The combined ethyl acetate extracts were washed with water, saturated sodium bicarbonate, and water. The combined extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a solid which was recrystallized from the ethyl acetate/hexane 1:1 v/v to afford 4-bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one: ^1H NMR (CDCl_3) δ 7.55 (dd, 1H, $J=2.7$, 9.0 Hz), 7.44 (dd, 1H, $J=8.7$, 5.1 Hz), 7.11 (Apparent dt,

1H, J=2.7, 4.8 Hz), 5.34¹⁸¹ (dd, 1H, J=5.7, 10.2 Hz),
3.20-2.50 (m, 4H).

4-Bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one was
5 similarly prepared from the corresponding ketone: ¹H NMR
(CDCl₃) δ 7.83 (d, 1H, J=7.8 Hz), 5.35 (dd, 1H, J=5.7, 10.5
Hz), 3.30-2.50 (m, 4H).

10 **General Procedure for the Synthesis of Boc Protected
Thioureas:**

A protected diamine such as N-Boc-1,4-diaminobutane or N-
Boc-1,5-diaminopentane (1 equivalent) was dissolved in
tetrahydrofuran and stirred at room temperature. Benzoyl
15 thioisocyanate (1 equivalent) was added dropwise to the
aforementioned solution. The resulting mixture was stirred
at room temperature for 24 hours. The solvent was removed
under reduced pressure to give a yellow oil.

20 The yellow oil (1 equivalent) was then dissolved in
methanol, an aqueous potassium carbonate (3 equivalents)
solution added, and the mixture stirred for 48 hours.
Water was added to the reaction mixture, which was then
extracted with 2x75 ml ethyl acetate. The combined
25 extracts were then washed with water, dried over anhydrous
sodium sulfate, filtered and the solvent removed under
reduced pressure to give the desired thiourea.

tert-Butyl 5-[(aminocarbothioyl)amino]pentylcarbamate was
30 obtained as a light yellow wax from tert-butyl 5-
{[(benzoylamino)carbothioyl]amino}-pentylcarbamate. ¹H NMR
(CD₃OD) δ 3.44 (m, 1H), 3.10 (m, 1H), 3.01 (t, 2H, J = 6.7
Hz), 1.60-1.31 (m, 6H), 1.41 (s, 9H); 262 (ESMS, MH⁺).

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tert-Butyl

5-

{[(benzoylamino)carbothioyl]amino}-pentylcarbamate was obtained a light yellow solid in 79% yield from N-BOC-1,5-diaminopentate and benzoyl isothiocyanate; m.p. 90-93 °C.

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tert-Butyl 4-[(aminocarbothioyl)amino]butylcarbamate was obtained as a light yellow wax from tert-butyl 4-{[(benzoylamino)carbothioyl]amino}-butylcarbamate. ¹H NMR (CD₃OD) δ 3.48 (m, 1H), 3.10 (m, 1H), 3.05 (t, 2H, J = 6.5 Hz), 1.60 (m, 4H), 1.42 (s, 9H); 248 (ESMS, MH⁺).

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tert-Butyl 4-{[(benzoylamino)carbothioyl]-amino}butylcarbamate was obtained as a light brown oil in 93% yield from N-BOC-1,4-diaminobutane and benzoyl isothiocyanate.

15

trans-tert-Butyl {4-[(aminocarbothioyl)amino]-cyclohexyl}methylcarbamate was obtained as a light yellow wax from trans-tert-butyl (4-{[(benzoylamino)carbothioyl]amino} cyclohexyl)-methylcarbamate. ¹H NMR (CD₃OD) δ 3.92 (m, 1H), 2.86 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.37 (m, 1H), 1.06 (m, 4H); 288 (ESMS, MH⁺).

20

trans-tert-Butyl- (4-{[(benzoylamino)carbothioyl]-amino}cyclohexyl)methylcarbamate was obtained as a yellow solid in 97% yield from tert-butyl 4-aminocyclohexylmethylcarbamate and benzoyl isothiocyanate.

25

trans-tert-Butyl 4-aminocyclohexylmethylcarbamate was obtained in more than 95 % yield from hydrogenation of benzyl 4-{[(tert-butoxycarbonyl)amino]methyl}-cyclocarbamate.

30

Benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate: To a stirred suspension of 4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexanecarboxylic acid (Maybridge Chemical Co., Ltd.) (45g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) was added triethylamine (32 ml) over a period of 20 min whilst maintaining the internal temperature at -10-0 C. The mixture was slowly warmed and then stirred at 70 C for 4h. After cooling to 40 C, benzyl alcohol (36 ml) was added and the reaction mixture heated at reflux for 20 h. The cold reaction mixture was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallization of the organic residue from ethyl acetate and diethyl ether gave the title compound, benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate as a white solid, m.p. 129-131 C.

trans-tert-Butyl 4-[[[aminocarbothioyl]amino]cyclohexyl]carbamate was obtained as a yellow solid from *trans*-tert-butyl 4-[[[benzoylamino]carbothioyl]amino]cyclohexyl)-carbamate: ¹H NMR (CD₃OD) δ 3.94 (m, 1H), 3.30 (m, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 1.41 (s, 9H), 1.26 (m, 4H); 274 (ESMS, MH⁺).

trans-tert-Butyl 4-[[[Benzoylamino]carbothioyl]amino]cyclohexyl)-carbamate was obtained as a white solid in 66% yield from *tert*-butyl 4-aminocyclohexylcarbamate and benzoyl isothiocyanate.

trans-tert-Butyl 4-aminocyclohexylcarbamate was obtained as a light yellow wax in more than 95% yield from

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hydrogenation of benzyl 4- [(tert-butoxycarbonyl)amino]cyclohexylcarbamate.

trans-Benzyl 4-{[(aminocarbothioyl)amino]methyl}cyclohexylcarbamate was obtained as a yellow solid in 71% yield from trans-benzyl 4-({[(Benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate; 322 (ESMS, MH⁺).

trans-Benzyl 4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate was obtained as a yellow solid from benzyl 4-(aminomethyl)cyclohexylcarbamate and benzoyl isothiocyanate.

trans-Benzyl 4-(aminomethyl)cyclohexylcarbamate was obtained as a white solid in more than 95% yield by stirring benzyl 4-{[(tert-butoxycarbonyl)amino]methyl}cyclocarbamate in 2N HCl (made from 1 : 1 of EtOAc and 4N HCl in dioxane).

20

General Procedure for the Synthesis of the (4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino Template.

A mixture of bromoketone (1 equivalent), thiourea (1 equivalent), and diisopropylethylamine (2 equivalents) in anhydrous ethanol was stirred and heated at reflux temperature overnight. The solvent was evaporated, the brown residue dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane three times. The combined extracts were dried over anhydrous sodium sulfate. The crude product was purified by flash column

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chromatography (silica gel, hexane : ethyl acetate). An example of the aforementioned general procedure follows.

4-Bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one (1.2 equivalents, 29.76 mmol) and tert-butyl 5-[(aminocarbothioyl)amino]pentylcarbamate (1 equivalent, 24.8 mmol) were mixed with 2 equivalents of diisopropylethylamine in 200 ml of EtOH. The reaction mixture was heated at reflux overnight. The dark brown reaction mixture was concentrated and chromatographed (silica) to obtain tert-butyl N-{5-[(9-fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}carbamate as a light tan solid.

General Procedure for the Deprotection of BOC-Protected Amines.

tert-Butyl N-{[4-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}carbamate or tert-butyl N-[6-(4,5-dihydrobenzo[2,3]thiepino-[4,5-d][1,3]thiazol-2-ylamino)hexyl]carbamate were dissolved in Et₂O. The same volume of 4N HCl in dioxane was added to make a 2N solution. The reaction mixture was stirred at room temperature overnight, and the solvent removed under reduced pressure to obtain the desired product as its HCl salt.

N1-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,4-butanediamine: 45% yield; ¹H NMR (CDCl₃) δ 8.05 (dd, 1H, J= 0.56, 8.4 Hz), 7.33 (dd, 1H, J= 0.6, 8.4 Hz), 7.26 (t, 1H, J=6.5 Hz), 7.17 (t, 1H, J=6.5 Hz), 5.91 (broad, 1H), 3.20 (m, 6H), 2.69 (t, 2H, J=6.5 Hz), 1.61-1.27 (m, 6H).

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N1-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,5-pentanediamine: 50% yield; ^1H NMR (CDCl_3) δ 8.03 (dd, 1H, $J=0.6, 8.4$ Hz), 7.49 (dd, 1H, $J=0.6, 8.4$ Hz), 7.28 (t, 1H, $J=6.5$ Hz), 7.16 (t, 1H, $J=6.5$ Hz), 5.92 (broad, 1H), 3.13 (m, 6H), 2.63 (t, 2H, $J=6.5$ Hz), 1.57-1.37 (m, 8H).

tert-Butyl N-{5-[(9-fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-carbamate: 60% yield; Anal. Calc. for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{F}_2\text{S}_2\text{O}_2 + 0.15 \text{CH}_2\text{Cl}_2$: C, 56.41; H, 6.33; N, 9.3. Found: C, 56.45; H, 6.17; N, 8.9; ^1H NMR (CDCl_3) δ 7.72 (dd, 1H, $J=1.15, 7.5$ Hz), 7.47-7.04 (m, 1H), 6.89-6.83 (m, 1H), 6.190-6.142 (m, 1H), 4.747-4.690 (m, 1H), 3.370-2.803 (m, 8H), 1.64-1.048 (m, 6H), 1.407 (s, 9H).

N2-[4-(Aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-amine: 73% yield, 346 (ESMS, MH^+); ^1H NMR (CDCl_3) δ 8.05 (dd, 1H, $J=1.2, 7.9$ Hz), 7.50 (dd, 1H, $J=1.2, 7.7$ Hz), 7.32 (apparent dt, 1H, $J=1.8, 7.2$ Hz), 7.15 (apparent dt, 1H, $J=1.7, 7.2$ Hz), 4.93 (b, 1H), 3.23 (m, 1H), 2.99 (t, 2H, $J=6.3$ Hz), 2.56 (d, 2H, $J=6.6$ Hz), 2.04 (ABM, 4H), 1.70-0.80 (m, 12H).

tert-Butyl N-[6-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]carbamate: 51% yield, 434 (ESMS, MH^+); ^1H NMR (CD_3OD) δ 7.92 (d, 1H, $J=7.5$ Hz), 7.48 (d, 1H, $J=7.6$ Hz), 7.30 (apparent dt, 1H, $J=1.2, 7.7$ Hz), 7.15 (apparent dt, 1H, $J=1.5, 7.5$ Hz), 3.30 (t, 2H, $J=1.6$ Hz), 3.16 (t, 2H, $J=6.3$ Hz), 3.05 (t, 2H, $J=5.9$ Hz), 3.01 (t, 2H, $J=6.5$ Hz), 1.63 (m, 2H), 1.42 (s, 9H), 1.51-1.28 (m, 6H).

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N1 - (4,5-

Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,6-

hexanediamine: 75% yield, 334 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.05 (dd, 1H, $J=1.0, 8.1$ Hz), 7.51 (dd, 1H, $J=1.1, 7.8$ Hz), 7.32 (apparent dt, 1H, $J=1.4, 7.4$ Hz), 7.15, (apparent dt, 1H, $J=1.6, 7.6$ Hz), 5.15 (broad, 1H), 3.23 (m, 4H), 3.19 (s, 2H), 2.68 (t, 2H, $J=5.7$ Hz), 1.70-1.21 (m, 8H).

10 tert-Butyl N-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}carbamate: 44% yield, 446 (ESMS, MH^+); 1H NMR (CD_3OD) δ 7.90 (dd, 1H, $J=1.2, 7.8$ Hz), 7.49 (dd, 1H, $J=0.8, 7.8$ Hz), 7.32 (apparent dt, 1H, $J=1.4, 7.7$ Hz), 7.16 (apparent dt, 1H, $J=1.3, 7.6$ Hz), 3.41 (m, 1H), 3.30 (m, 2H), 3.19 (t, 2H, $J=6.5$ Hz), 3.06, (t, 2H, $J=5.8$ Hz), 2.90 (d, 2H, $J=7.0$ Hz), 1.99 (ABm, 4H), 1.43 (s, 9H), 1.32-1.05 (m, 3H).

20 **General Procedure for the Derivatization of Amines with Sulfamoyl Chlorides:**

An amine such as N1 - (4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,6-hexanediamine or N2 - [4-(aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-amine (0.305 mmol) was dissolved in 2ml CH_2Cl_2 with 2 equivalents of diisopropylethylamine. A sulfamoyl chloride (1-3 equivalents) was added dropwise. The reaction solution was stirred at room temperature for 3 days, quenched with water, washed with 10% $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and chromatographed using column chromatography or preparative TLC.

Alternatively, a diamine such as 1,4-bis-aminomethylcyclohexane was derivatized with a sulfamyl chloride which was then derivatized to yield a sulfonyl urea followed by cyclization using a bromoketone as exemplified below:

N'-[4-(Aminomethyl)cyclohexyl]methyl-*N,N*-dimethylsulfamide: A solution of 1,4-bis-aminomethylcyclohexane in 50 ml of dichloromethane was treated dropwise with 8.0 grams of neat dimethylaminosulfamoyl chloride. The resulting mixture was stirred at room temperature for 24 hours, washed with water and chromatographed (silica) to give 10 grams (25% yield) of *N'*-[4-(aminomethyl)cyclohexyl]methyl-*N,N*-dimethylsulfamide: ¹H NMR (CDCl₃) δ 3.00 (d, 2H, J=7.5 Hz), 2.78 (s, 6H), 3.60 (d, 2H, J=7.5), 1.85-1.22 (m, 8H), 1.00-0.80 (m, 1H).

N-Benzoyl-*N'*-[4-([(dimethylamino)sulfonyl]aminomethyl)-cyclohexyl]methylthiourea and *N*-[4-([(dimethylamino)-sulfonyl]aminomethyl)cyclohexyl]methylthiourea: A solution of 1.0 g of *N'*-[4-(aminomethyl)cyclohexyl]-methyl-*N,N*-dimethylsulfamide in 25 ml of THF was treated with 0.7 g of benzoylisothiocyanate, stirred for 24 hours and the solvent removed to afford a crude product: ¹H NMR (CDCl₃) δ 8.20-7.60 (m, 5H), 3.80-3.30 (broad, 3H), 2.80-2.60 (m, 2H), 2.55-2.40 (m, 2H), 2.00-1.20 (m, 17H), 1.00-0.80 (m, 2H).

The crude product was treated with 15 ml of methanol and 15 ml of water containing 2.0 g of potassium carbonate. The mixture was stirred for 24 hours and then extracted with

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ethyl acetate. The combined extracts were washed with saturated NaCl solution, dried (sodium sulfate) and the solvent removed under reduced pressure to give a yellow oil which was used in the next step without further purification.

N'-(4-[(4,5-Dihydrobenzo[2,3]thiepino[4,5-*d*][1,3]thiazol-2-ylamino)methyl]cyclohexylmethyl)-*N,N*-dimethylsulfamide: 4-Bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one (.200 g, 0.720 mmole) and *N*-[4-[(dimethylamino)sulfonyl]aminomethyl]-cyclohexyl]methylthiourea (0.250 g, 0.810 mmole) were heated at reflux for 18 hours, the solvent removed under reduced pressure and the crude product chromatographed (silica) to afford *N'*-(4-[(4,5-dihydrobenzo[2,3]thiepino[4,5-*d*][1,3]thiazol-2-ylamino)methyl]cyclohexylmethyl)-*N,N*-dimethylsulfamide.

The following examples were prepared according to the reaction sequence shown in Schemes 12, 13 and 14 which describe the synthesis of carbamates and sulfonylureas:

Example 100

tert-Butyl *N*-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-*d*][1,3]thiazol-2-ylamino)cyclohexyl]methyl}carbamate: 44% yield, 446 (ESMS, MH^+); 1H NMR (CD_3OD) δ 7.90 (dd, 1H, $J=1.2, 7.8$ Hz), 7.49 (dd, 1H, $J=0.8, 7.8$ Hz), 7.32 (apparent dt, 1H, $J=1.4, 7.7$ Hz), 7.16 (apparent dt, 1H, $J=1.3, 7.6$ Hz), 3.41 (m, 1H), 3.30 (m, 2H), 3.19 (t, 2H, $J=6.5$ Hz), 3.06 (t, 2H, $J=5.8$ Hz), 2.90 (d, 2H, $J=7.0$ Hz), 1.99 (ABm, 4H), 1.43 (s, 9H), 1.32-1.05 (m, 3H).

Example 101

N' - [6 - (4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl] - N,N-diethylsulfamide:

5 72% yield, 470 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.05 (dd, 1H, J=1.3, 8.0 Hz), 7.52 (dd, 1H, J=0.8, 7.2 Hz), 7.33 (apparent dt, 1H, J=0.8, 8.0 Hz), 7.16 (apparent dt, 1H, J=1.3, 7.2 Hz), 5.05 (m, 1H), 4.02 (m, 1H), 3.26 (q, 4H, J=7.1 Hz), 3.29-3.22 (m, 2H), 3.20 (s, 2H), 2.97 (q, 2H, 10 J=6.7 Hz), 1.67-1.37 (m, 10H), 1.81 (t, 6H, J=7.1 Hz).

Example 102

N' - { [4 - (4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol- 15 2-ylamino)cyclohexyl]methyl} - N,N-diethylsulfamide: 84% yield, 481 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.05 (dd, 1H, J=1.0, 8.0 Hz), 7.52 (dd, 1H, J=0.9, 7.7 Hz), 7.33 (apparent dt, 1H, J=1.0, 7.7 Hz), 7.16 (apparent dt, 1H, J=7.7 Hz), 4.86 (m, 1H), 4.04 (m, 1H), 3.27 (q, 4H, J=7.5 20 Hz), 3.20 (m, 1H), 3.19 (s, 2H), 2.86 (t, 2H, J=6.8 Hz), 2.08 (ABm, 4H), 1.52 (m, 2H), 1.20 (t, 6H, J=7.5 Hz), 1.10 (m, 5H).

Example 103

25 N' - [5 - (4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl] - N,N-diethylsulfamide: 55% yield; Anal. Calc. for C₂₀H₃₀N₄S₃O₂ + 0.1 CH₂Cl₂: C, 52.12; H, 6.57; N, 12.10. Found: C, 52.13; H, 6.12; N, 11.96; ¹H NMR (CDCl₃) δ 30 8.02 (dd, 1H, J=0.6, 7.5 Hz), 7.50 (dd, 1H, J=0.6, 7.5 Hz), 7.31 (t, 1H, J=6.5 Hz), 7.15 (t, J=6.5 Hz), 6.00 (broad, 1H), 4.85 (m, 1H), 3.27-3.11 (m, 10H), 2.87-2.85 (m, 2H), 1.52-1.18 (m, 12H).

Example 104

N'-[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)butyl]-N,N-diethylsulfamide: 45% yield; Anal.
5 Calc. for $C_{19}H_{28}N_4S_3O_2 + 0.2 CH_2Cl_2$: C, 50.39; H, 6.25; N 12.24. Found: C, 50.75; H, 6.17; N, 11.96. 1H NMR ($CDCl_3$) δ 7.99 (dd, 1H, J=0.6, 7.5 Hz), 7.50 (dd, 1H, J=0.6, 7.5 Hz), 7.31 (t, 1H, J=6.5 Hz), 7.15 (t, 1H, J=6.5 Hz), 6.17 (broad, 1H), 5.08 (m, 1H), 3.08-3.26 (m, 10H), 2.81 (m,
10 2H), 1.44-1.12 (m, 10H).

Example 105

tert-Butyl N-{5-[(9-fluoro-4,5-dihydrobenzo[2,3]-
15 thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-carbamate:
60% yield; Anal. Calc. for $C_{21}H_{28}N_3FS_2O_2 + 0.15 CH_2Cl_2$: C, 56.41; H, 6.33; N, 9.30. Found : C, 56.45; H, 6.17; N, 8.90; 1H NMR ($CDCl_3$) δ 7.72 (dd, 1H, J=1.2, 7.5 Hz), 7.47-7.04 (m, 1H), 6.89-6.83 (m, 1H), 6.190-6.142 (m, 1H),
20 4.747-4.690 (m, 1H), 3.37-2.80 (m, 8H), 1.64-1.05 (m, 6H), 1.41 (s, 9H).

Example 106

25 N'-[4-[(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexylmethyl]-N,N-dimethylsulfamide:
50% yield; Anal. Calc. For $C_{21}H_{29}F_1N_4S_3O_2$: C, 52.00; H, 6.0; N, 11.5. Found: C, 51.76; H, 6.41; N, 11.05; 1H NMR ($CDCl_3$)
30 δ 7.70 (dd, 1H, J=4.3 Hz), 7.50-7.40 (m, 1H), 6.87-6.80 (m, 1H), 6.40-6.32 (broad, 1H), 5.20-5.05 (m, 1H), 3.20-3.00 (m, 6H), 2.90-2.82 (m, 2H), 2.78 (s, 6H), 1.80-1.22 (m, 8H), 1.00-0.78 (m, 2H).

II. Synthetic Methods for General Structures

A. Tricyclic Compounds

The examples described in Section IA are merely illustrative of the methods used to synthesize tricyclic compounds in Section A of the Summary Of The Invention and Detailed Description Of The Invention. Further compounds may be obtained utilizing methods shown in Schemes 1-6. The substituents in Schemes 1-6 are described in the Detailed Description.

10

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form tricyclic derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

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B. Bicyclic Compounds

The examples described in Section IB are merely illustrative of the methods used to synthesize bicyclic derivatives in Section B of the Summary Of The Invention and Detailed Description Of The Invention. Further derivatives may be obtained utilizing methods shown in Schemes 7-11. The substituents in Schemes 7-11 are described in the Detailed Description.

30

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form bicyclic derivatives. Methods for protection and deprotection of

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such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

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C. Tricyclic Compounds

The examples described in Section IC are merely illustrative of the methods used to synthesize tricyclic compounds in Section C of the Summary Of The Invention and
10 Detailed Description Of The Invention. Further compounds may be obtained utilizing methods shown in Schemes 12-17. The substituents in Schemes 12-17 are described in the Detailed Description.

15 It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form tricyclic derivatives. Methods for protection and deprotection of
20 such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

III. Oral Compositions

25 As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg
30 to fill a size 0 hard gel capsule.

IV. Pharmacological Evaluation of Compounds at Cloned Neuropeptide Y-type Receptors

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The pharmacological properties of the compounds of the present invention were evaluated at one or more of the cloned human neuropeptide Y-type receptors Y1, Y2, Y4, and Y5, using protocols described below.

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Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO₂. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO₂. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LM(tk-) cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin/100 µg/mL streptomycin) at 37 °C, 5% CO₂. Stock plates of LM(tk-) cells were trypsinized and split 1:10 every 3-4 days.

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LM(tk-) cells stably transfected with the human Y5 receptor were routinely converted from an adherent monolayer to a viable suspension. Adherent cells were harvested with trypsin at the point of confluence, resuspended in a minimal volume of complete DMEM for a cell count, and further diluted to a concentration of 10⁶ cells/ml in suspension media (10% bovine calf serum, 10% 10X Medium 199 (Gibco), 9 mM NaHCO₃, 25 mM glucose, 2 mM L-glutamine, 100 units/ml penicillin/100 µg/ml

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streptomycin, and 0.05% methyl cellulose). The cell suspension was maintained in a shaking incubator at 37 °C, 5% CO₂ for 24 hours. Membranes harvested from cells grown in this manner may be stored as large, uniform batches in liquid nitrogen. Alternatively, cells may be returned to adherent cell culture in complete DMEM by distribution into 96-well microtiter plates coated with poly-D-lysine (0.01 mg/ml) followed by incubation at 37 °C, 5% CO₂ for 24 hours. Cells prepared in this manner yielded a robust and reliable NPY-dependent response in cAMP radio-immunoassays as further described hereinbelow.

Mouse embryonic fibroblast NIH-3T3 cells were grown on 150 mm plates in Dulbecco's Modified Eagle Medium (DMEM) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO₂. Stock plates of NIH-3T3 cells were trypsinized and split 1:15 every 3-4 days.

Sf9 and Sf21 cells were grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27 °C, no CO₂. High Five insect cells were grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at 27 °C, no CO₂.

Transient Transfection

All receptor subtypes studied (human and rat Y1, human and rat Y2, human and rat Y4, human and rat Y5) were transiently transfected into COS-7 cells by the DEAE-dextran method, using 1 µg of DNA /10⁶ cells (Cullen, 1987). The human Y1 receptor was prepared using known methods (Larhammar, et al., 1992).

Stable Transfection

Human Y1, human Y2, and rat Y5 receptors were co-transfected with a G-418 resistant gene into the human embryonic kidney 293 cell line by a calcium phosphate transfection method (Cullen, 1987). Stably transfected cells were selected with G-418. Human Y4 and human Y5 receptors were similarly transfected into mouse fibroblast LM(tk-) cells and NIH-3T3 cells.

Binding of the compounds of the present invention to human Y1, Y2, Y4, and Y5 receptors was evaluated using stably transfected 293 or LM(tk-) cells as described above. Stably transfected cell lines which may be used for binding assays include, for example, for the human Y1 receptor, 293-hY1-5 (deposited June 4, 1996, under ATCC Accession No. CRL-12121), for the human Y2 receptor, 293-hY2-10 (deposited January 27, 1994, under ATCC Accession No. CRL-11537), for the human Y4 receptor, L-hY4-3 (deposited January 11, 1995, under ATCC Accession No. CRL-11779), and for human Y5 receptor, L-hY5-7 (deposited November 15, 1995, under ATCC Accession No. CRL-11995). These cell lines were deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

Membrane Harvest

Membranes were harvested from COS-7 cells 48 hours after transient transfection. Adherent cells were washed twice in ice-cold phosphate buffered saline (138 mM NaCl, 8.1 mM Na₂HPO₄, 2.5 mM KCl, 1.2 mM KH₂PO₄, 0.9 mM CaCl₂, 0.5 mM MgCl₂, pH 7.4) and lysed by sonication in ice-cold

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sonication buffer (20 mM Tris-HCl, 5 mM EDTA, pH 7.7). Large particles and debris were cleared by low speed centrifugation (200 x g, 5 min, 4 °C). Membranes were collected from the supernatant fraction by centrifugation (32,000 x g, 18 min, 4 °C), washed with ice-cold hypotonic buffer, and collected again by centrifugation (32,000 x g, 18 min, 4 °C). The final membrane pellet was resuspended by sonication into a small volume of ice-cold binding buffer (~1 ml for every 5 plates: 10 mM NaCl, 20 mM HEPES, 0.22 mM KH₂PO₄, 1.26 mM CaCl₂, 0.81 mM MgSO₄, pH 7.4). Protein concentration was measured by the Bradford method (Bradford, 1976) using Bio-Rad Reagent, with bovine serum albumin as a standard. Membranes were held on ice for up to one hour and used fresh, or flash-frozen and stored in liquid nitrogen.

Membranes were prepared similarly from 293, LM(tk-), and NIH-3T3 cells. To prepare membranes from baculovirus infected cells, 2 x 10⁷ Sf21 cells were grown in 150mm tissue culture dishes and infected with a high-titer stock of hY5BB3. Cells were incubated for 2-4 days at 27 °C, no CO₂ before harvesting and membrane preparation as described above.

Membranes were prepared similarly from dissected rat hypothalamus. Frozen hypothalami were homogenized for 20 seconds in ice-cold sonication buffer with the narrow probe of a Virtishear homogenizer at 1000 rpm (Virtis, Gardiner, NY). Large particles and debris were cleared by centrifugation (200 x g, 5 min, 4 °C) and the supernatant fraction was reserved on ice. Membranes were further extracted from the pellet by repeating the homogenization and centrifugation procedure two more times. The supernatant fractions were pooled and subjected to high

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speed centrifugation (100,000 x g, 20 min. 4 °C).
The final membrane pellet was resuspended by gentle
homogenization into a small volume of ice-cold binding
buffer (1 mL/gram wet weight tissue) and held on ice for
up to one hour, or flash-frozen and stored in liquid
nitrogen.

Radioligand Binding to Membrane Suspensions

Membrane suspensions were diluted in binding buffer
supplemented with 0.1% bovine serum albumin to yield an
optimal membrane protein concentration so that ^{125}I -PYY (or
alternative radioligand such as ^{125}I -NPY, ^{125}I -PYY₃₋₃₆, or
 ^{125}I -[Leu³¹Pro³⁴]PYY) bound by membranes in the assay was
less than 10% of ^{125}I -PYY (or alternative radioligand)
delivered to the sample (100,000 dpm/sample = 0.08 nM for
competition binding assays). ^{125}I -PYY (or alternative
radioligand) and peptide competitors were also diluted to
desired concentrations in supplemented binding buffer.
Individual samples were then prepared in 96-well
polypropylene microtiter plates by mixing ^{125}I -PYY (25 μL)
(or alternative radioligand), competing peptides or
supplemented binding buffer (25 μL), and finally, membrane
suspensions (200 μL). Samples were incubated in a 30 °C
water bath with constant shaking for 120 min. Incubations
were terminated by filtration over Whatman GF/C filters
(pre-coated with 1% polyethyleneimine and air-dried before
use), followed by washing with 5 mL of ice-cold binding
buffer. Filter-trapped membranes were impregnated with
MeltiLex solid scintillant (Wallac, Turku, Finland) and
counted for ^{125}I in a Wallac Beta-Plate Reader.
Alternatively, incubations were carried out in GF/C filter
plates (pre-coated with 1% polyethyleneimine and air-dried
before use), followed by vacuum filtration and three
washes of 300 μL of ice-cold binding buffer. 50 μL of

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UltimaGold (Packard) scintillant were added and counted for ^{125}I in a Wallac MicroBeta Trilux. Non-specific binding was defined by 300 nM human NPY for all receptors except the Y4 subtypes; 100 nM human PP was used for the human Y4 and 100 nM rat PP for the rat Y4. Specific binding in time course and competition studies was typically 80%; most non-specific binding was associated with the filter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Radioimmunoassay of cAMP

Stably transfected cells were seeded into 96-well microtiter plates and cultured until confluent. To reduce the potential for receptor desensitization, the serum component of the media was reduced to 1.5% for 4 to 16 hours before the assay. Cells were washed in Hank's buffered saline, or HBS (150 mM NaCl, 20 mM HEPES, 1 mM CaCl_2 , 5 mM KCl, 1 mM MgCl_2 , and 10 mM glucose) supplemented with 0.1% bovine serum albumin plus 5 mM theophylline and pre-equilibrated in the same solution for 20 min at 37 °C in 5% CO_2 . Cells were then incubated 5 min with 10 μM forskolin and various concentrations of receptor-selective ligands. The assay was terminated by the removal of HBS and acidification of the cells with 100 mM HCl. Intracellular cAMP was extracted and quantified with a modified version of a magnetic bead-based radioimmunoassay (Advanced Magnetix, Cambridge, MA). The final antigen/antibody complex was separated from free ^{125}I -cAMP by vacuum filtration through a PVDF filter in a microtiter plate (Millipore, Bedford, MA). Filters were punched and counted for ^{125}I in a Packard gamma counter. Binding data were analyzed using nonlinear regression and

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statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Intracellular calcium mobilization

5 The intracellular free calcium concentration was measured by microspectrofluorometry using the fluorescent indicator dye Fura-2/AM. Stably transfected cells were seeded onto a 35 mm culture dish containing a glass coverslip insert. 10 Cells were washed with HBS and loaded with 100 μ l of Fura-2/AM (10 μ M) for 20 to 40 min. After washing with HBS to remove the Fura-2/AM solution, cells were equilibrated in HBS for 10 to 20 min. Cells were then visualized under the 40X objective of a Leitz Fluovert FS microscope and 15 fluorescence emission was determined at 510 nM with excitation wave lengths alternating between 340 nM and 380 nM. Raw fluorescence data were converted to calcium concentrations using standard calcium concentration curves and software analysis techniques.

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Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and 96-well microtiter) were from Corning (Corning, NY). Sf9, 25 Sf21, and High Five insect cells, as well as the baculovirus transfer plasmid, pBlueBacIIITM, were purchased from Invitrogen (San Diego, CA). TMN-FH insect medium complemented with 10% fetal calf serum, and the baculovirus DNA, BaculoGoldTM, was obtained from Pharmingen 30 (San Diego, CA.). Ex-Cell 400TM medium with L-Glutamine was purchased from JRH Scientific. Polypropylene 96-well microtiter plates were from Co-star (Cambridge, MA). All radioligands were from New England Nuclear (Boston, MA). Commercially available NPY and related peptide analogs 35 were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA); [D-Trp³²]NPY and PP C-terminal

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fragments were synthesized by custom order from Chiron
Mimotopes Peptide Systems (San Diego, CA). Bio-Rad Reagent
was from Bio-Rad (Hercules, CA). Bovine serum albumin
(kdfjas;jflka;ljf;dalkjf;lkajf;lka(ultra-fat free, A-7511)
5 was from Sigma (St. Louis. MO).1 other materials were
reagent grade.

Radioligand Binding Assay Results

10 The compounds described above were assayed using cloned
human NPY receptors. The preferred compounds were found
to be selective NPY (Y5) antagonists. The binding
affinities of several compounds for NPY (Y5) are
illustrated in Tables 1-3.

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Table 1

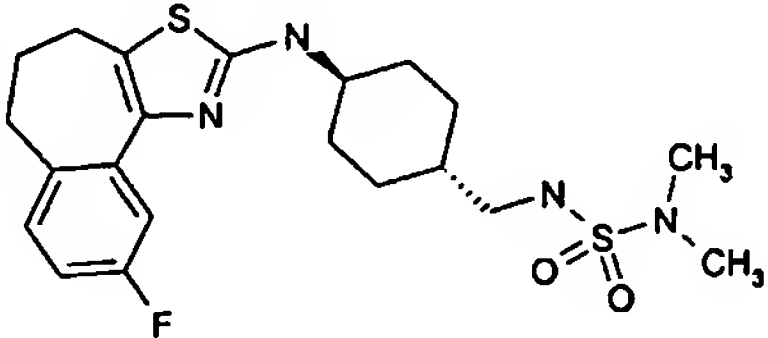
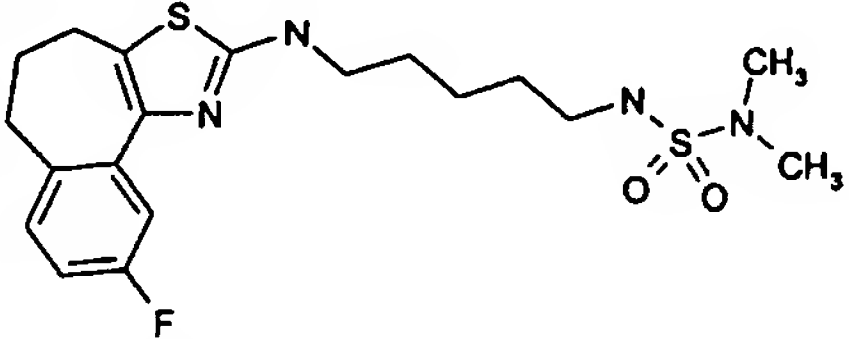
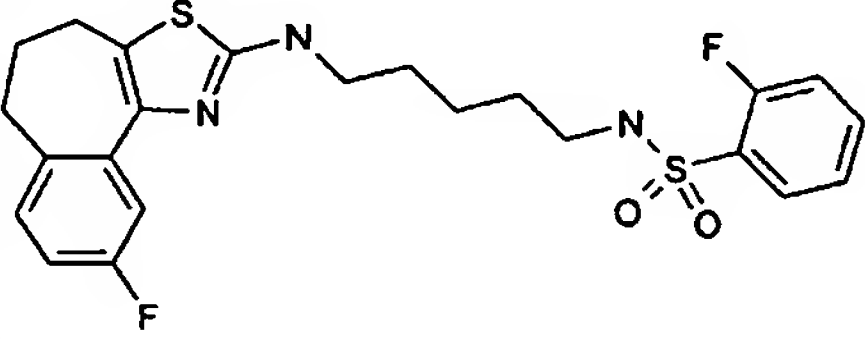
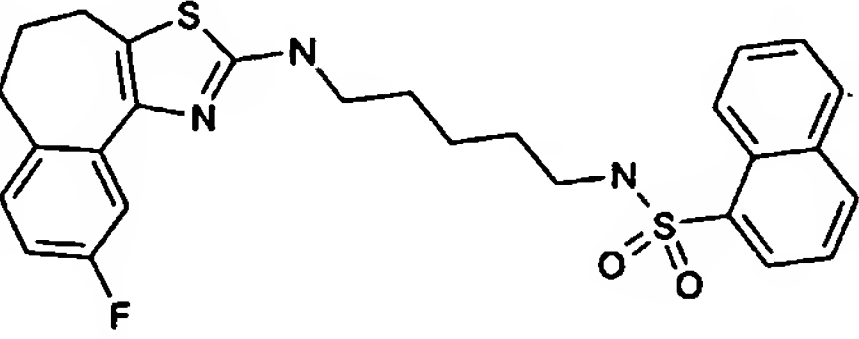
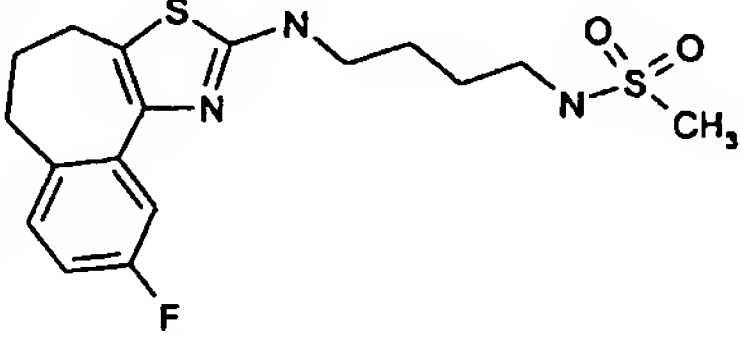
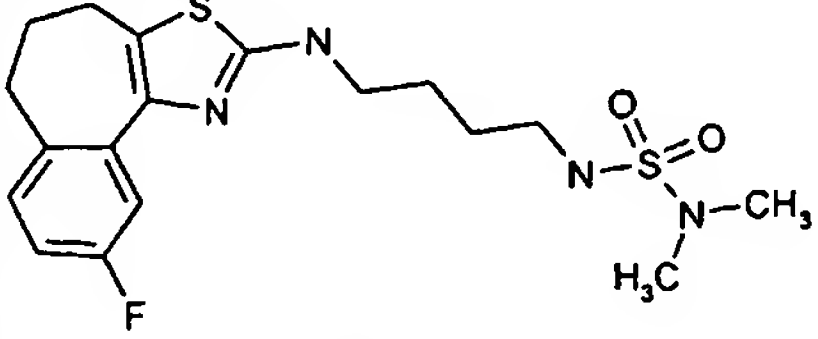
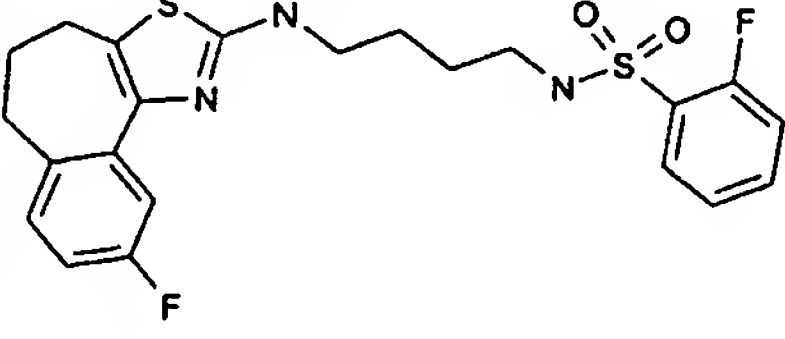
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2		1.6	
3		4.5	>10000
4		19.5	>10000
5		19.8	>10000
6		3.1	
7		23	>10000

Table 1 continued

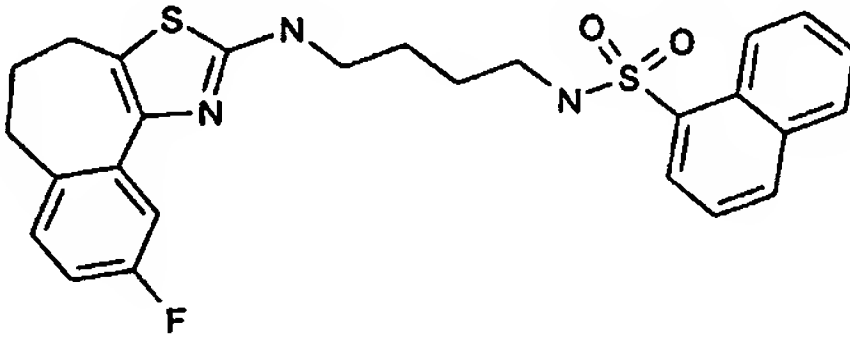
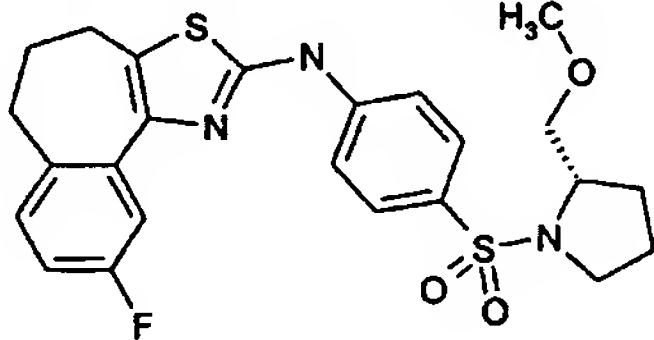
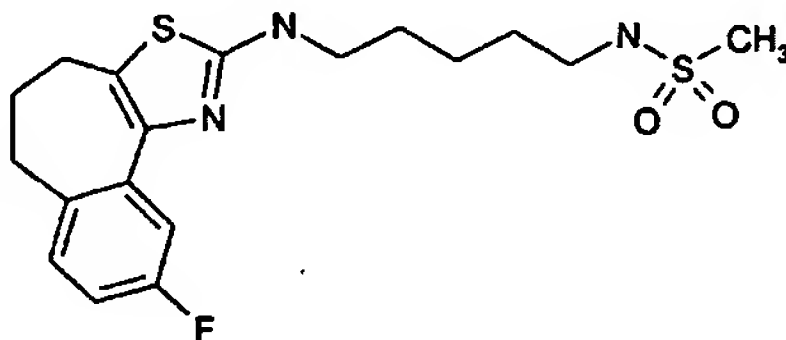
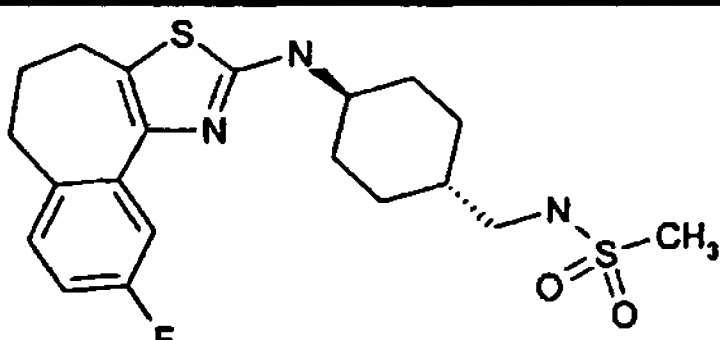
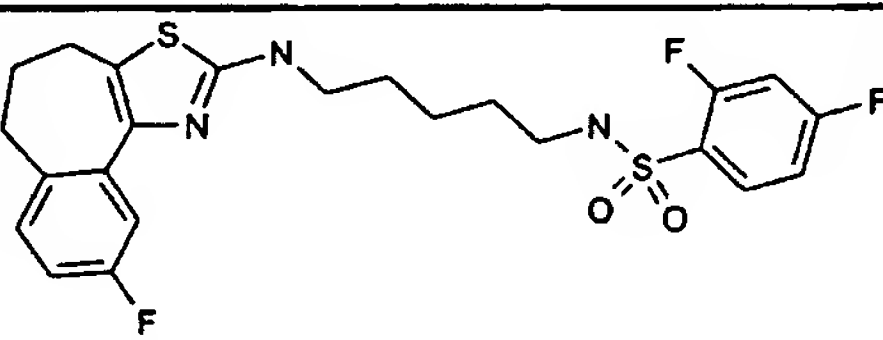
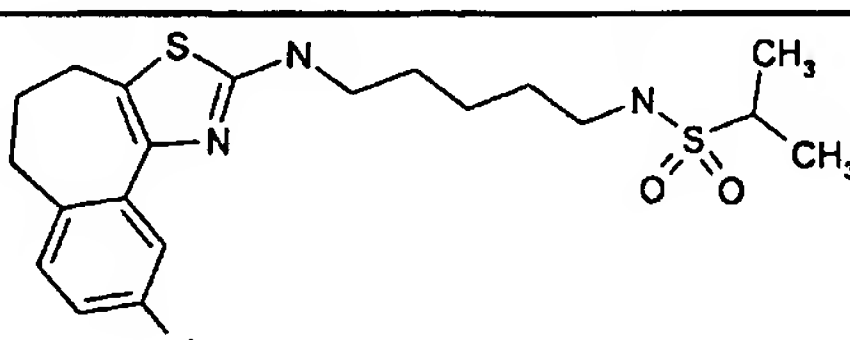
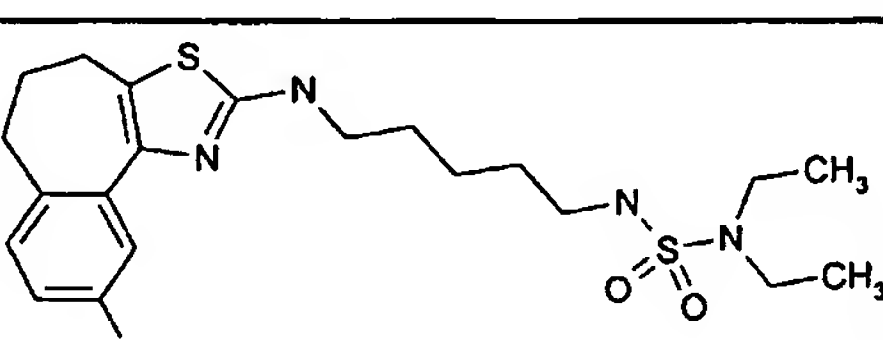
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8		94	
9		15.4	>10000
10		2.4	>10000
11		6.4	>10000
12		6.1	>1000
13		132	
14		2.1	>10000

Table 1 continued

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
15		3.2	
16		4.7	>10000
17		11	>10000
18		7.1	>10000
19		5	>10000
20		5.8	>10000
21		2.5	>10000

Table 1 continued

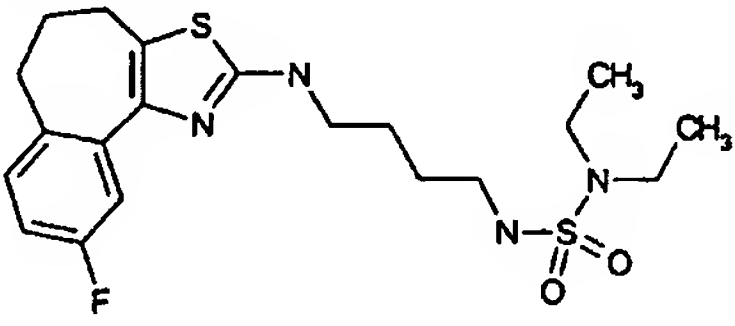
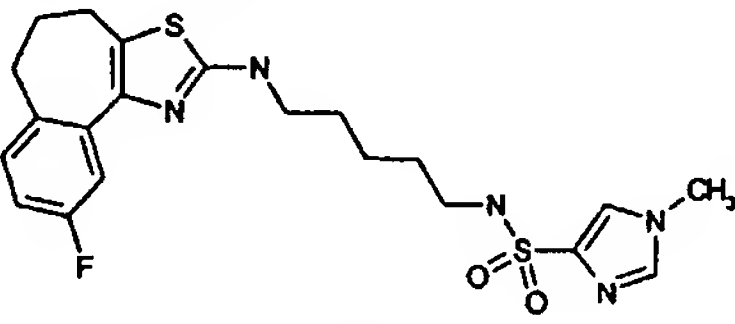
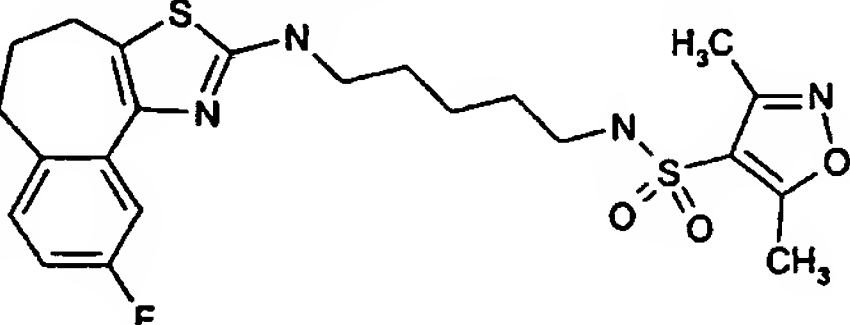
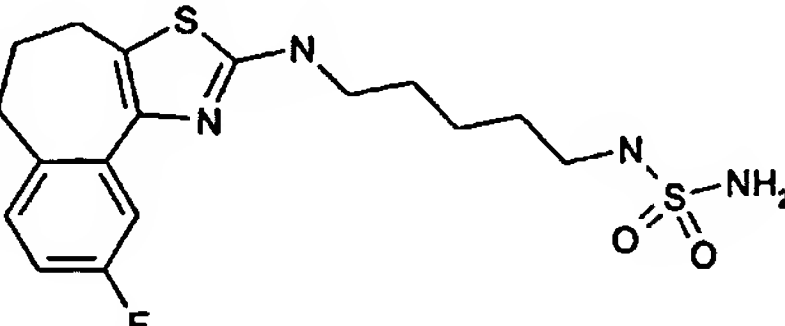
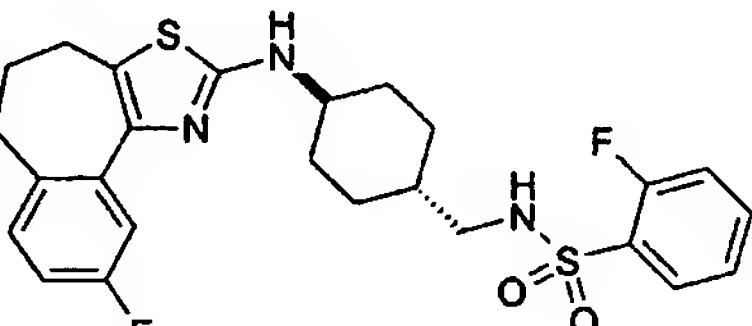
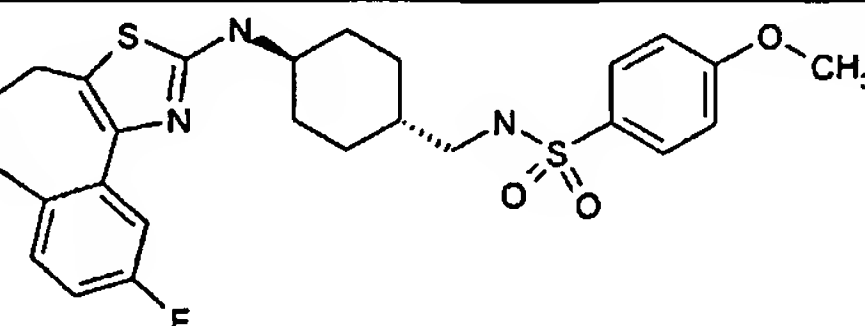
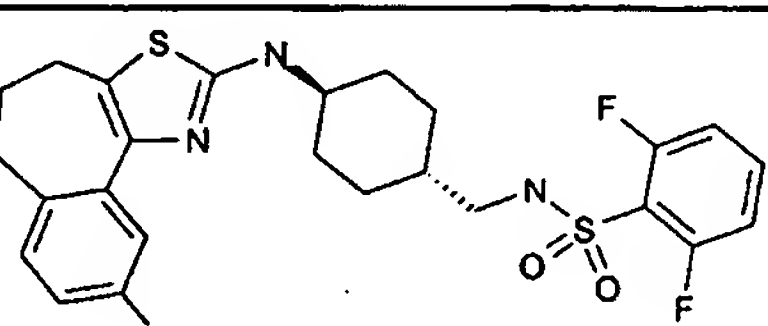
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22		2.9	>10000
23		15.5	>10000
24		3.5	>10000
25		2.9	>10000
26		13.1	>10000
27		9.2	>10000
28		4	>10000

Table 1 continued

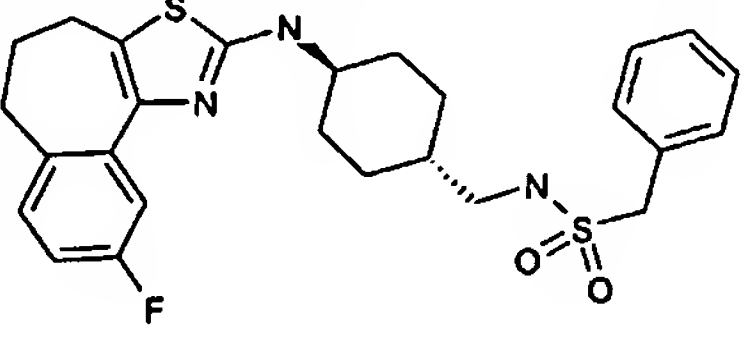
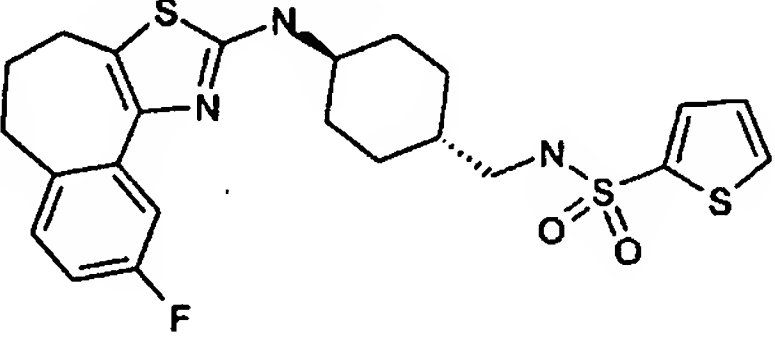
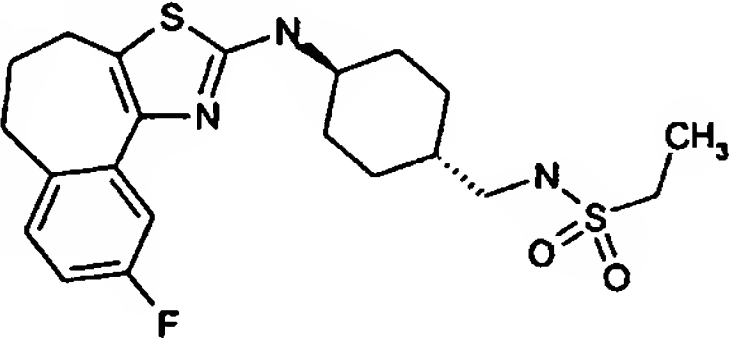
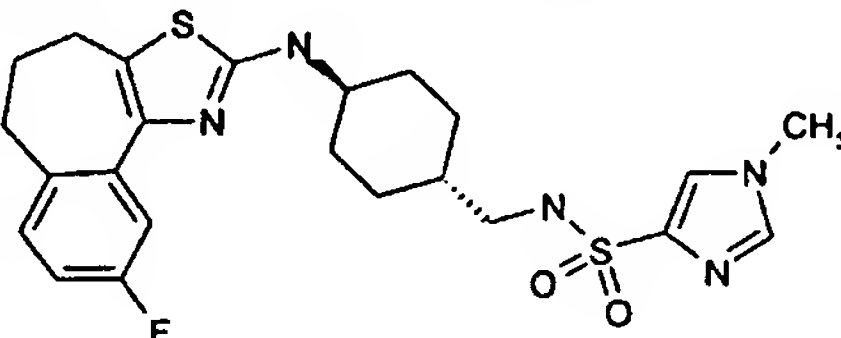
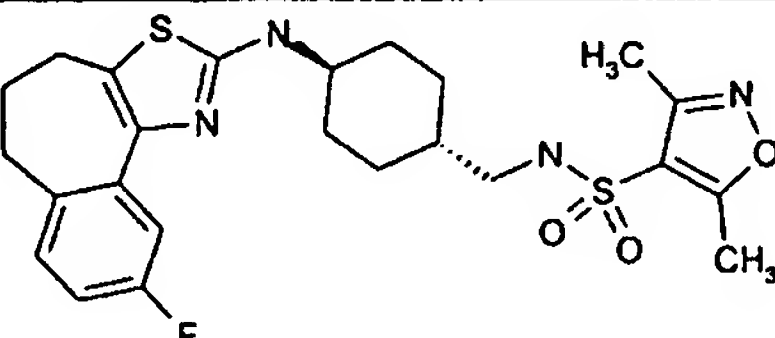
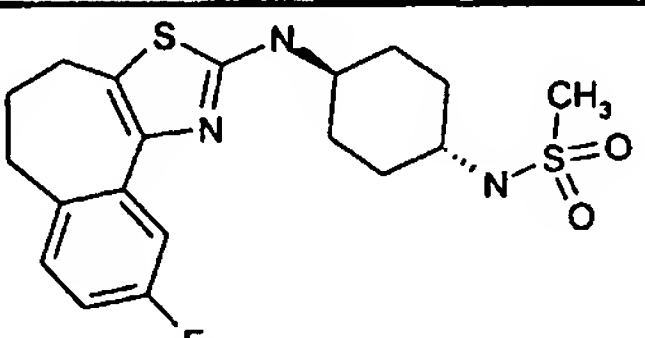
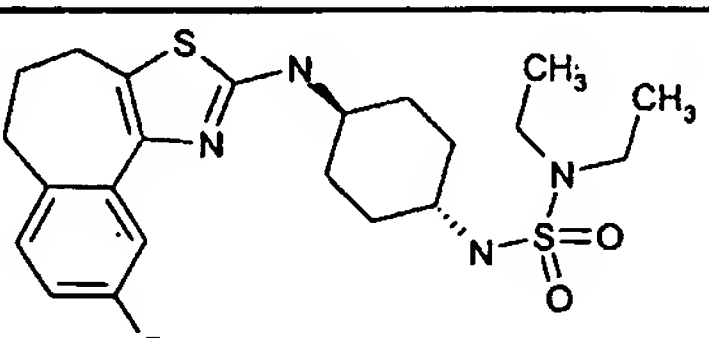
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30		4.2	>10000
31		3.9	>10000
32		2.9	>10000
33		6.8	>10000
34		34	
35		6.5	>10000

Table 1 continued

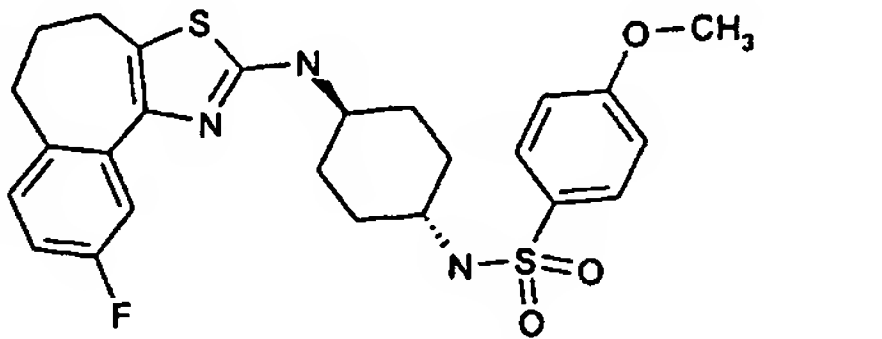
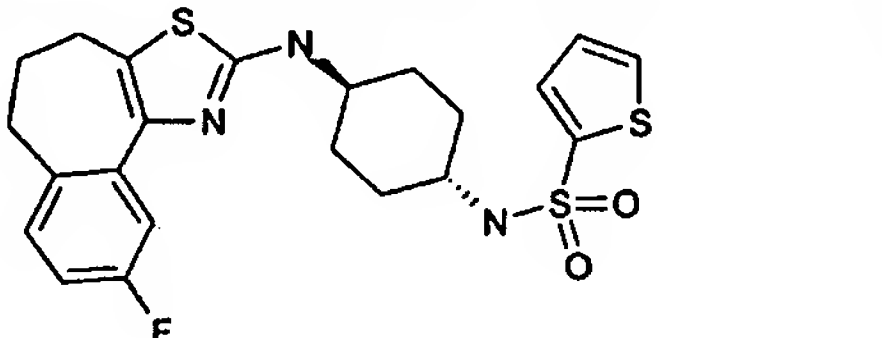
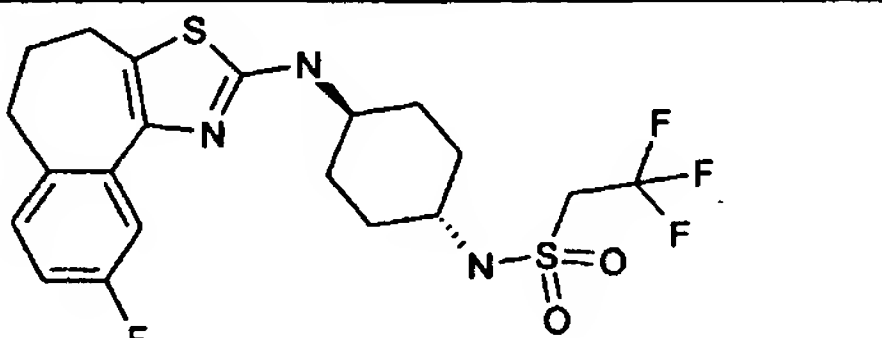
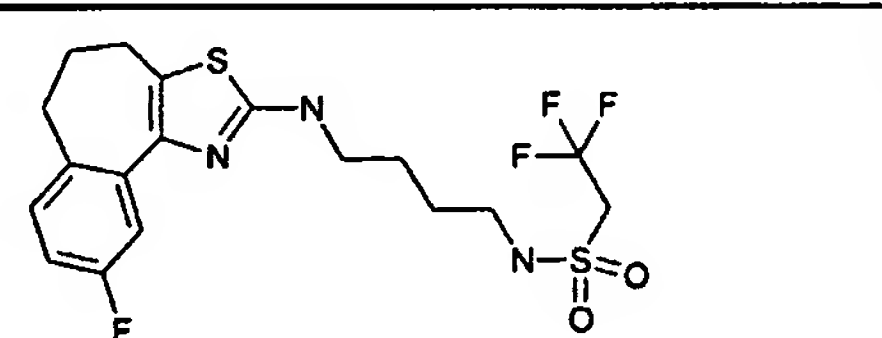
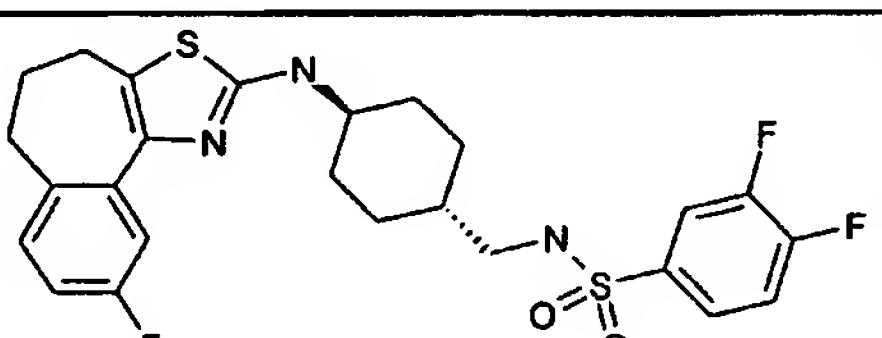
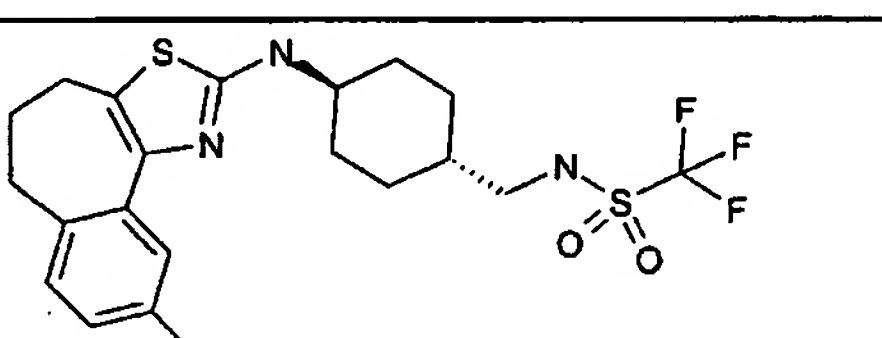
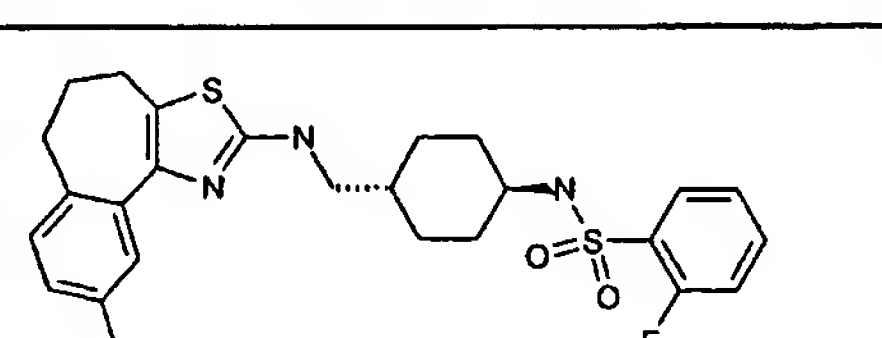
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37		7.4	>10000
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39		4.8	>10000
40		19.5	>10000
41		30	
42		3.9	>10000

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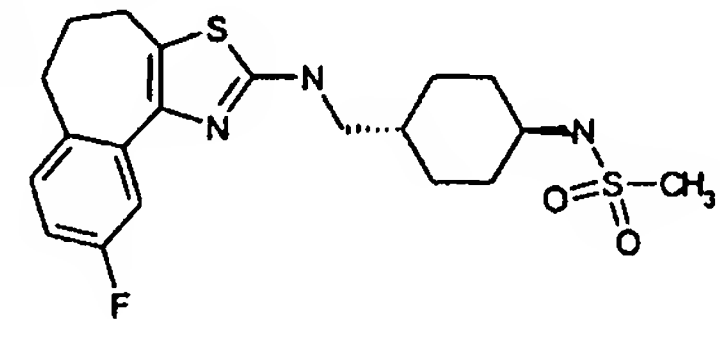
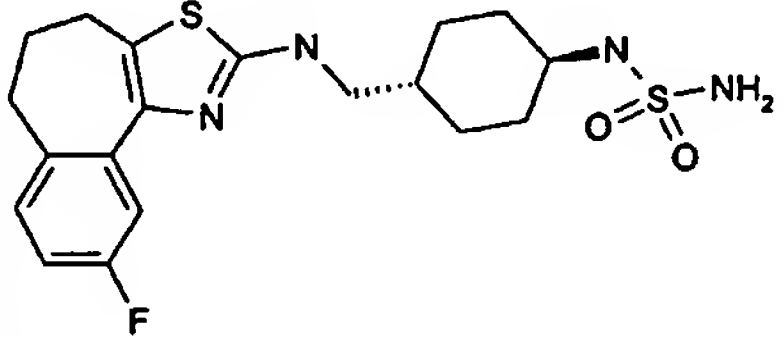
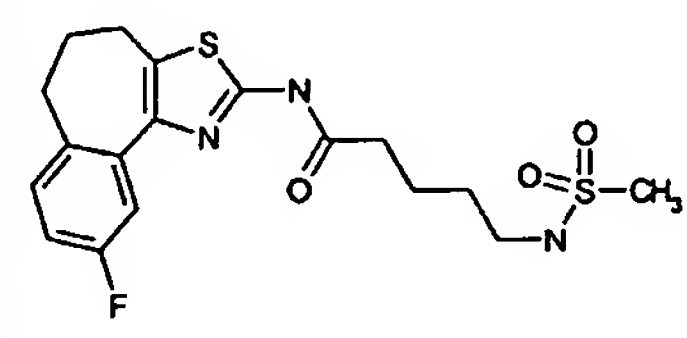
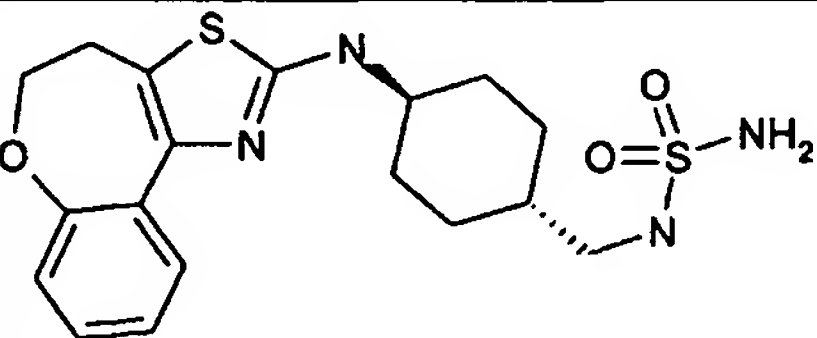
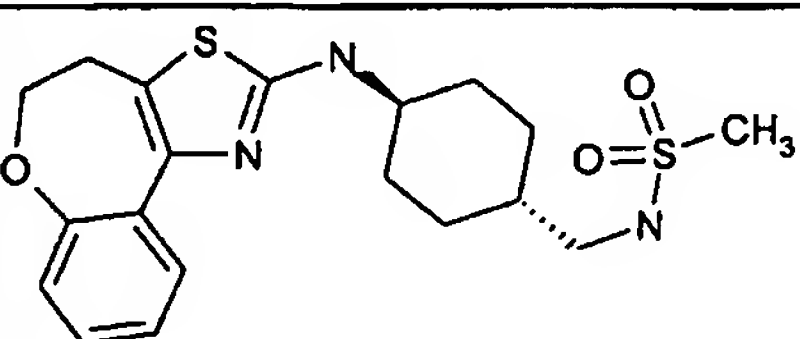
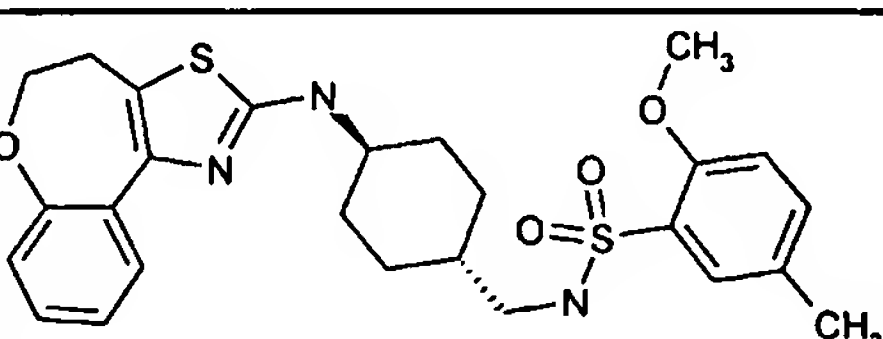
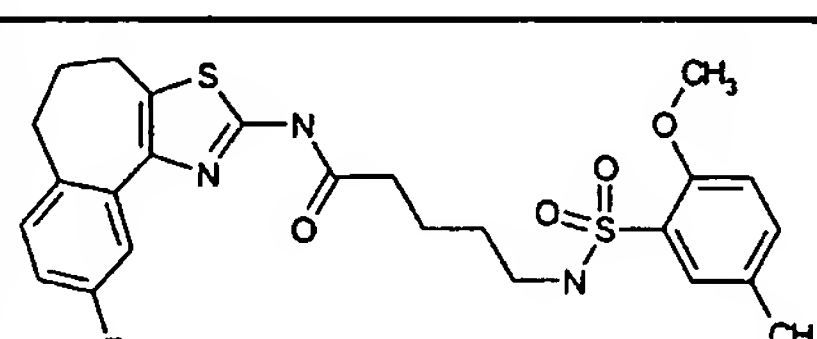
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46		34	>10000
47		22	>10000
48		15.1	>10000
49		2.9	

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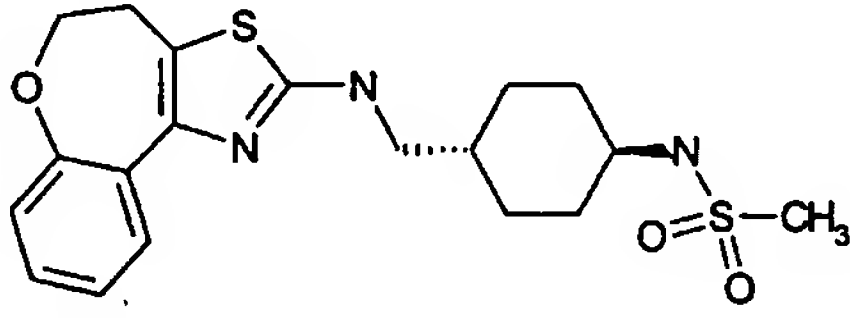
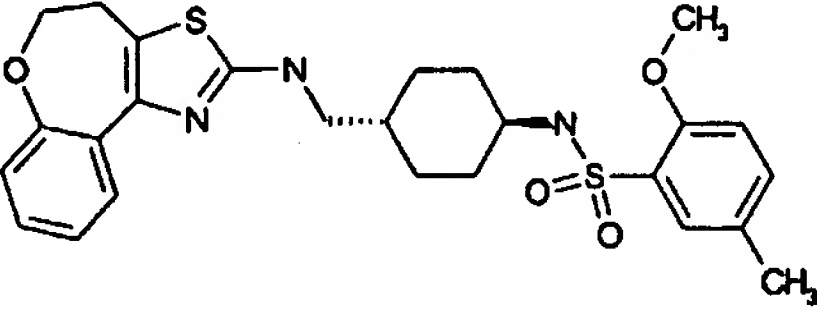
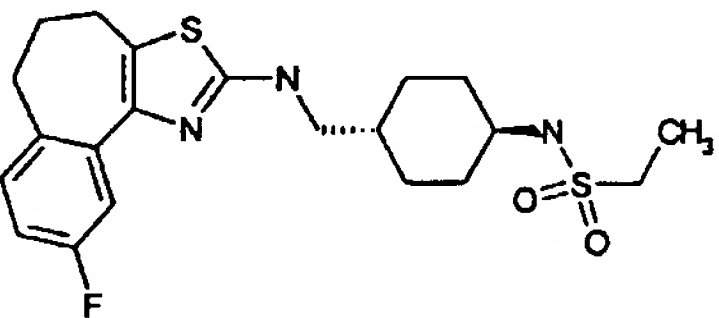
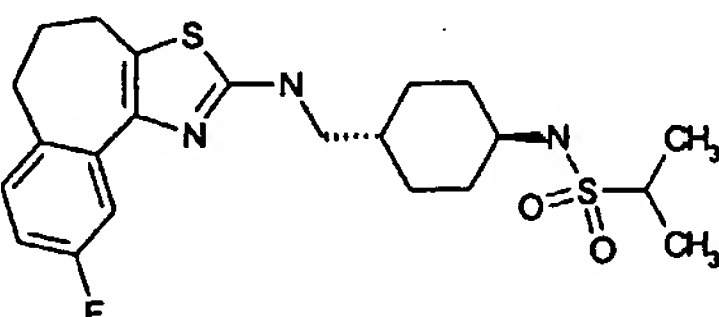
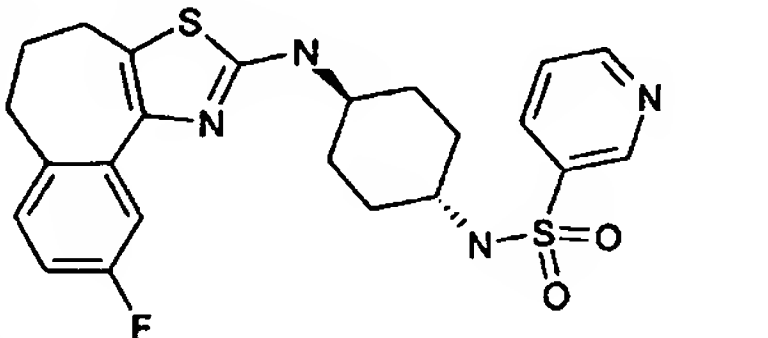
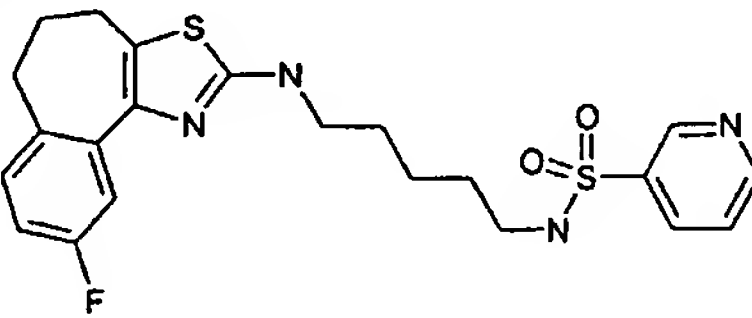
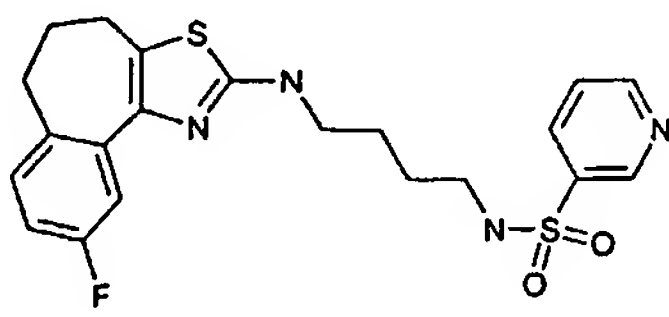
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
50		15.3	
51		8.3	
52		1.7	
53		3.2	
54		11.9	>10000
55		3.4	
56		26	

Table 1 continued

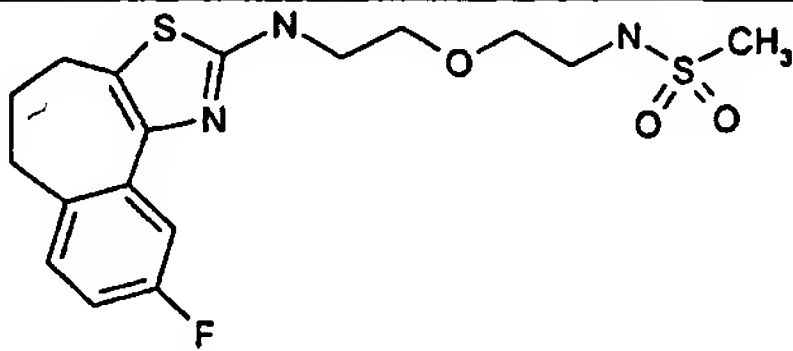
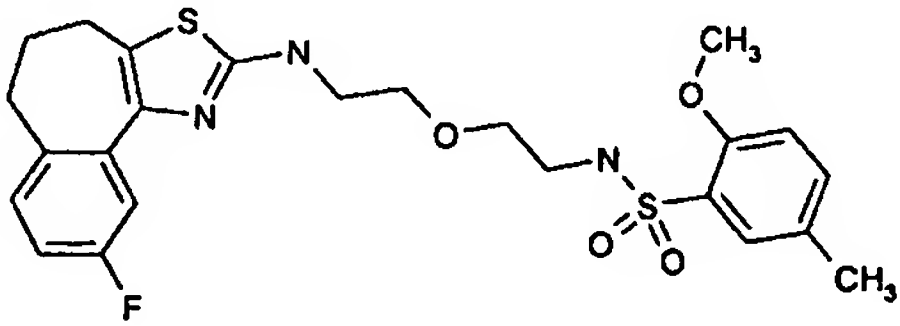
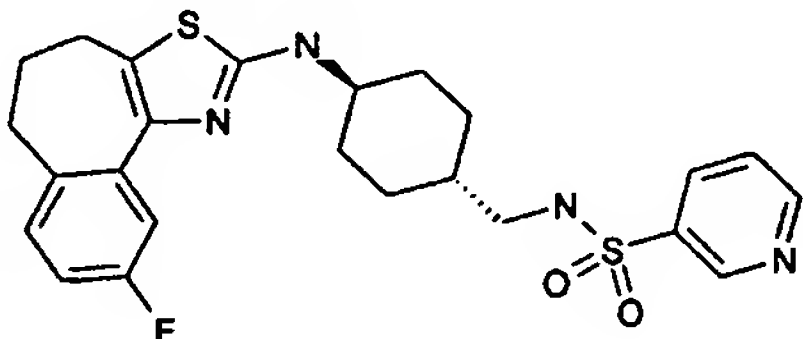
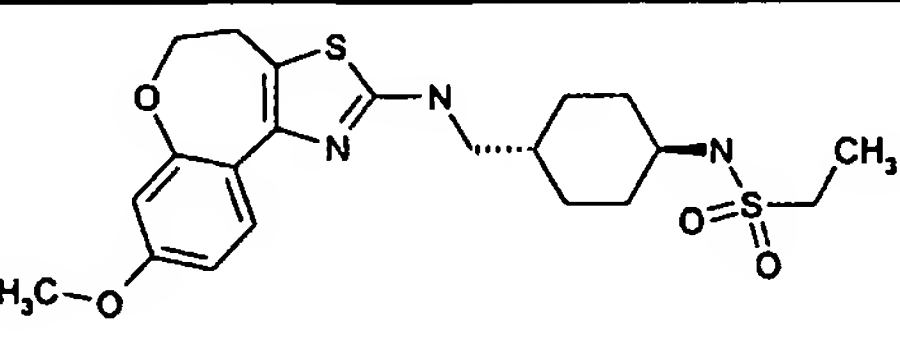
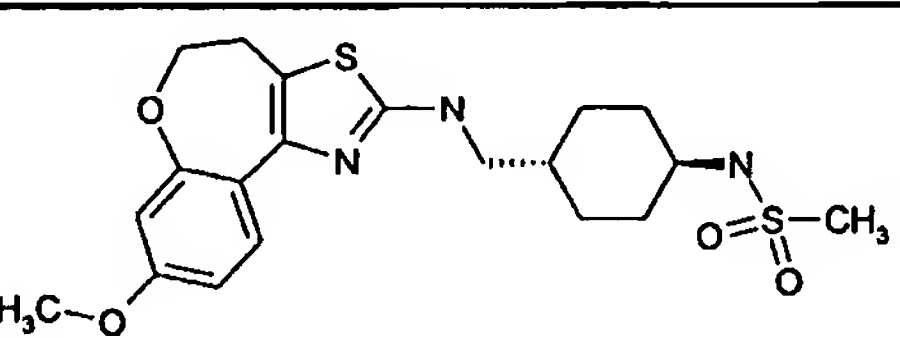
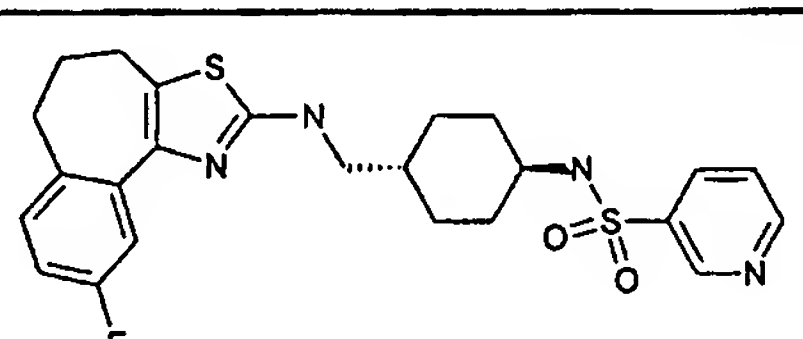
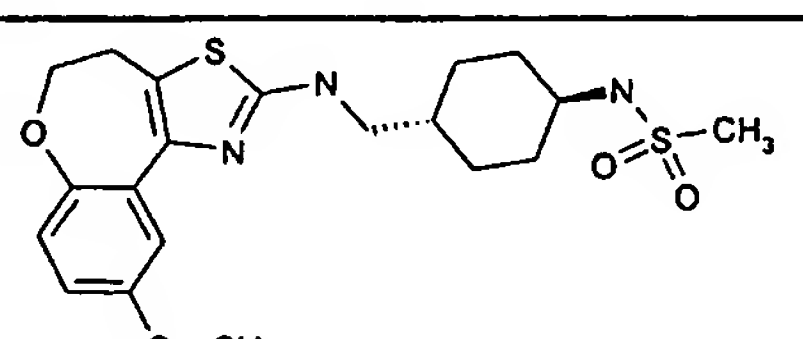
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
57		66	
58		3	
59		2.3	
60		31	
61		162	
62		1.8	
63		31	

Table 1 continued

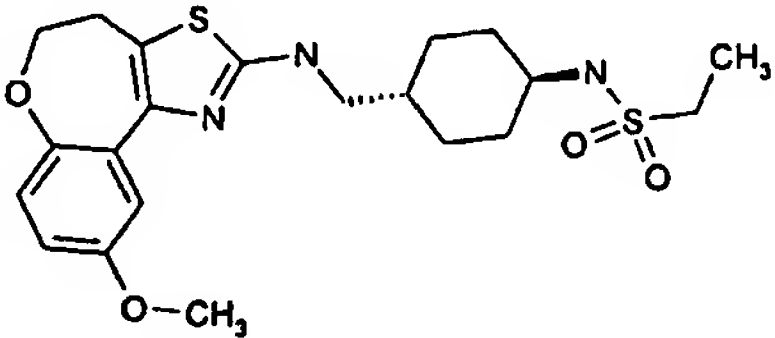
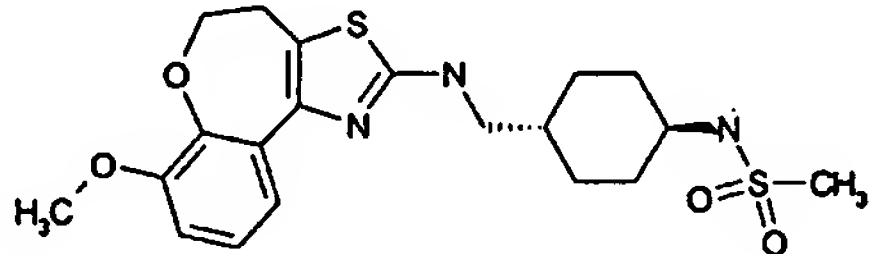
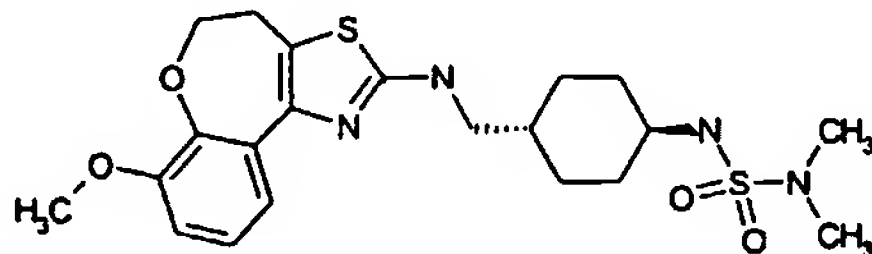
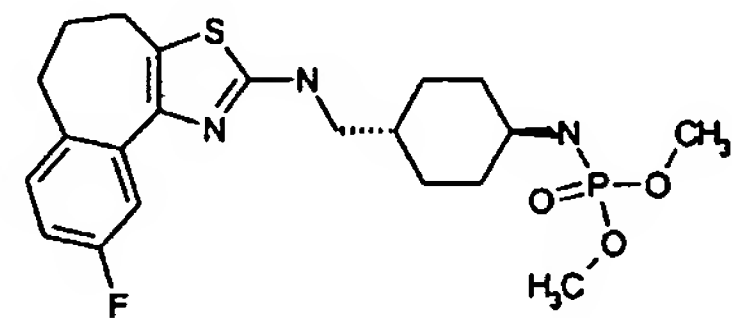
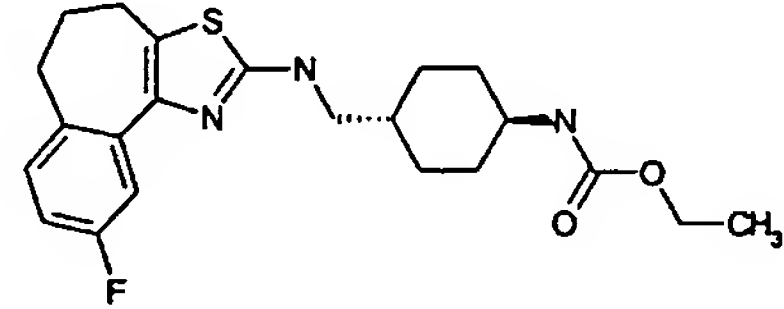
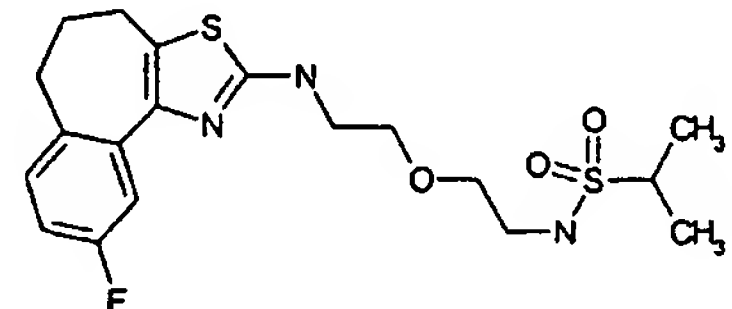
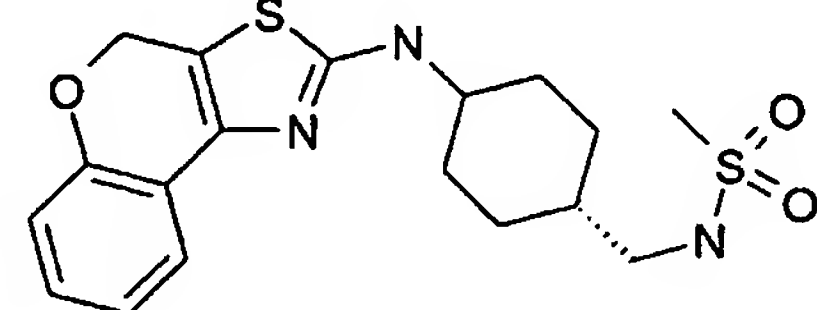
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
64		12.2	
65		11.6	
66		2	
67		5.5	
68		4	
69		4.1	
70		21	

Table 1 continued

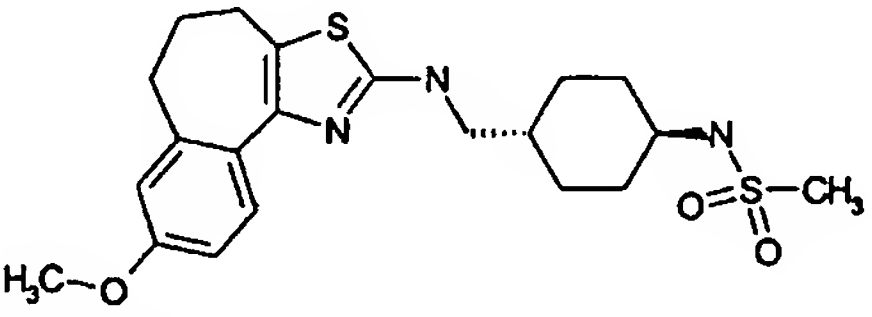
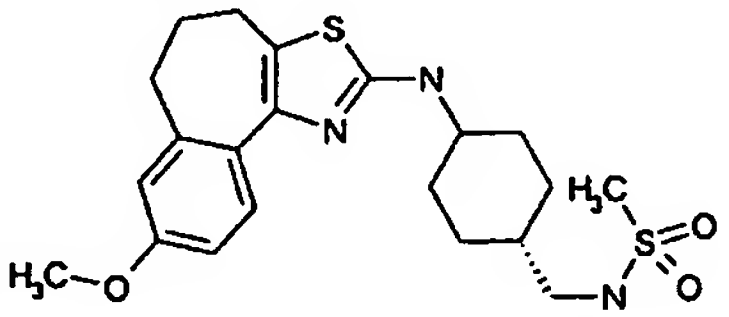
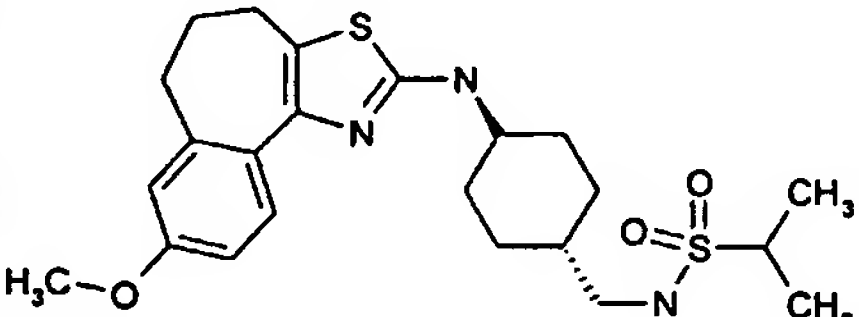
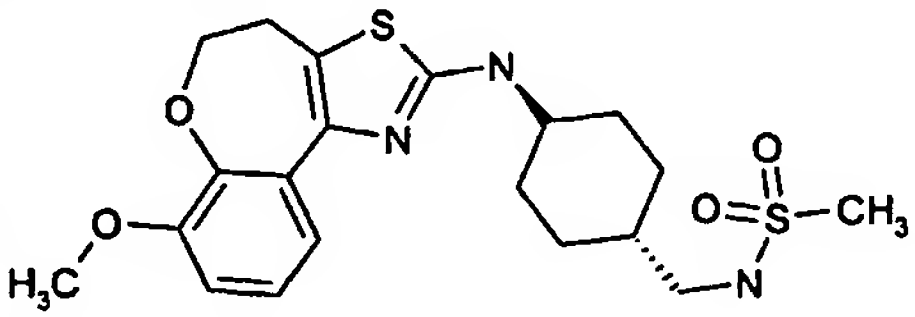
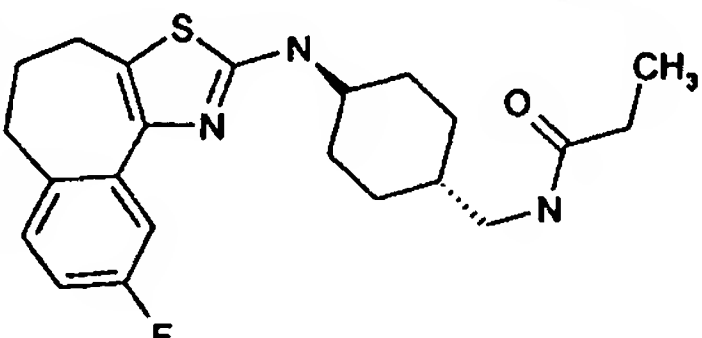
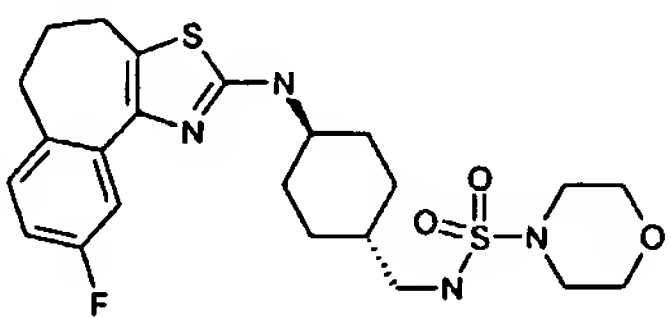
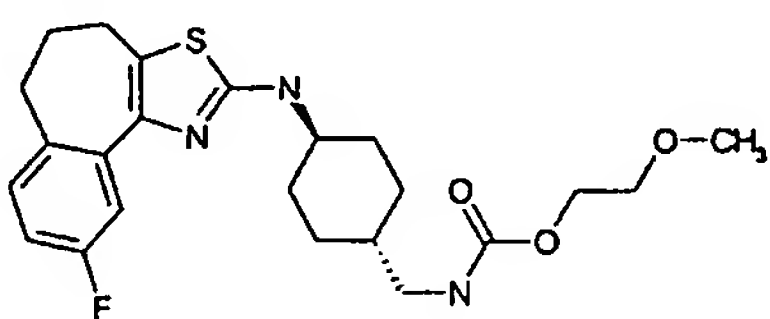
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1, 2, 4
71		2.5	
72		22	
73		8.7	
74		37	
75		36	
76		4.1	
77		14.6	

Table 1 continued

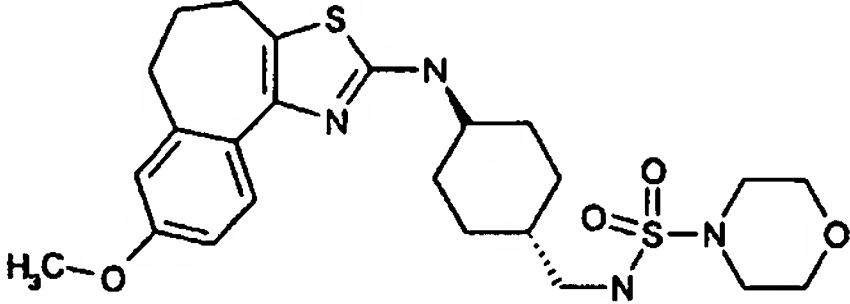
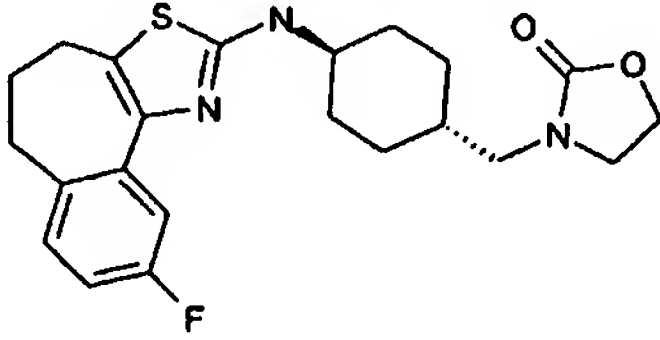
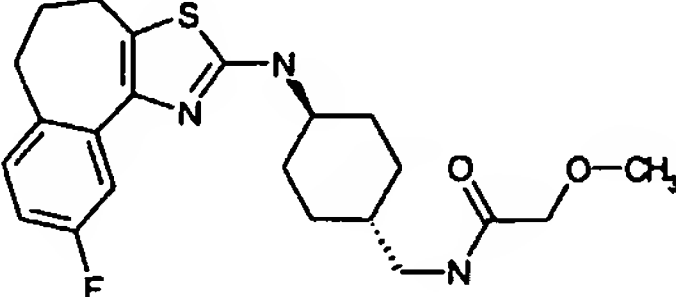
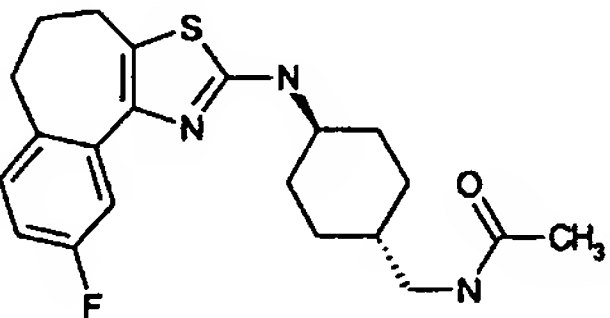
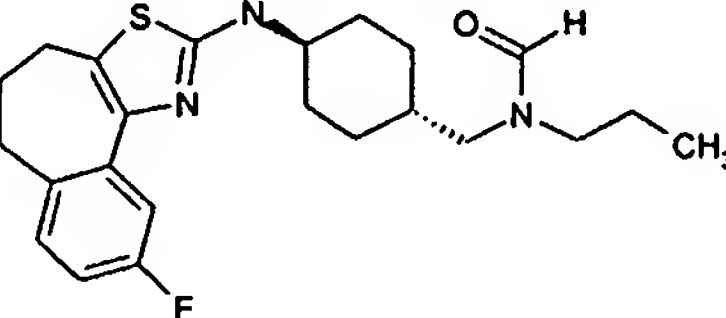
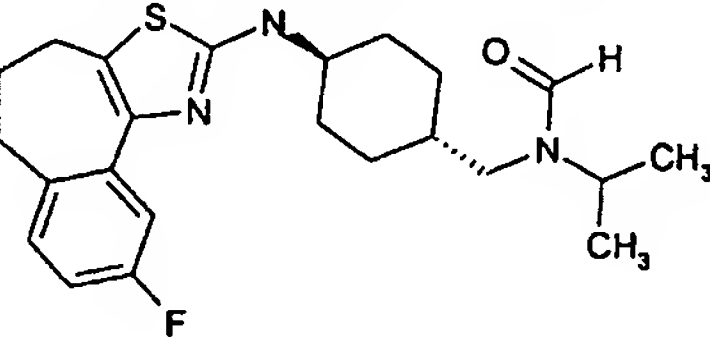
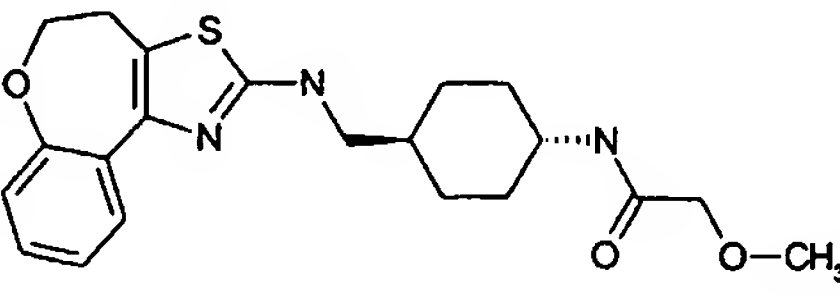
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
78		6	
79		20	
80		33	
81		62	
82		11.9	
83		12	
84		40	

Table 1 continued

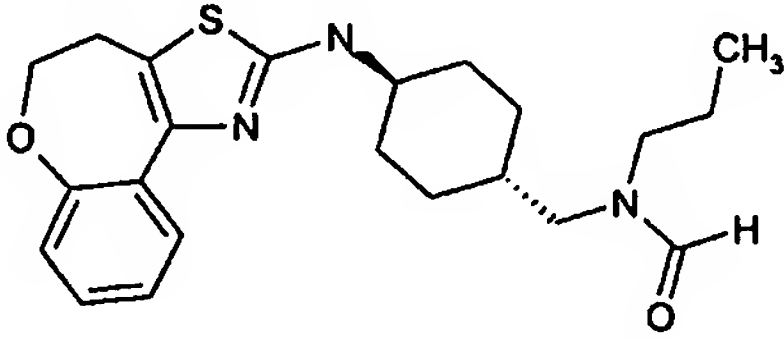
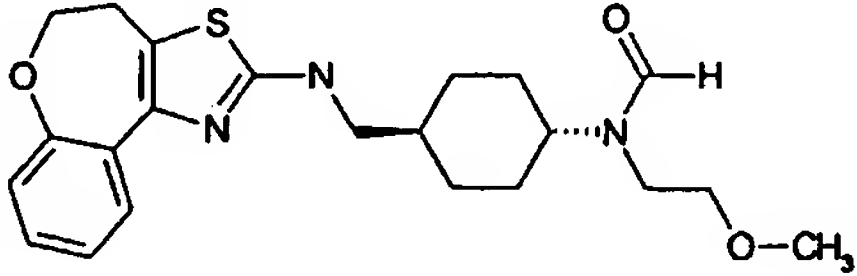
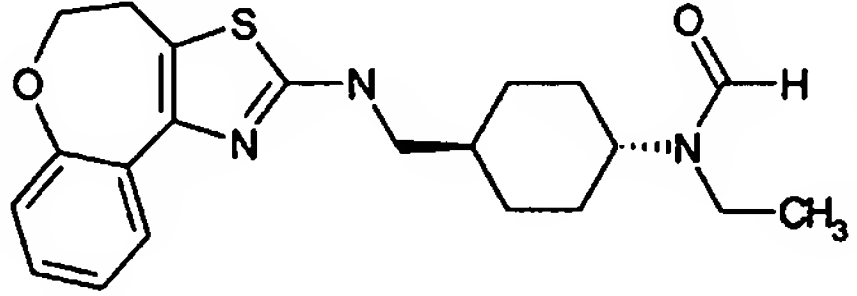
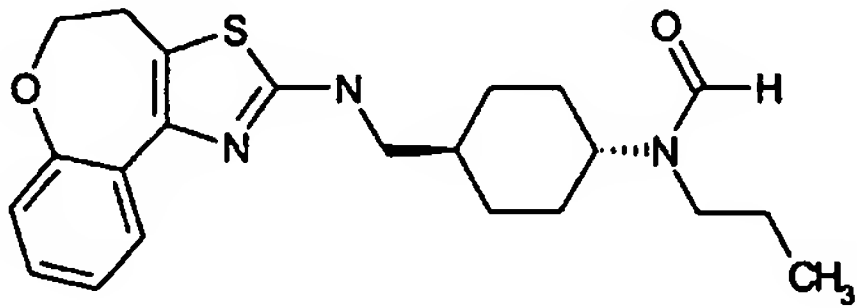
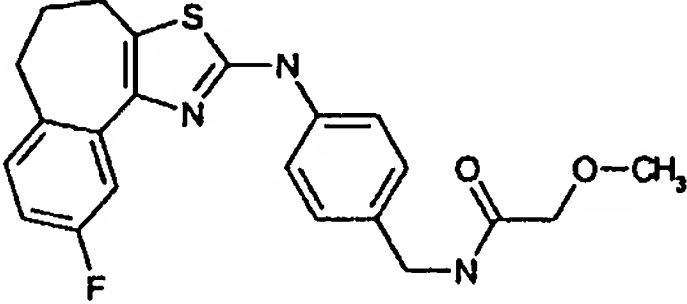
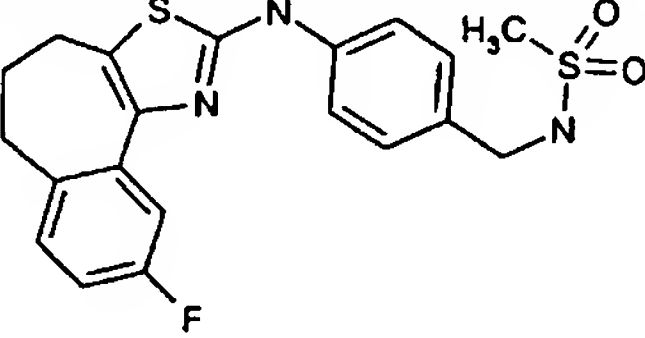
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
85		150	
86		68	
87		86	
88		36	
89		9.2	
90		5.7	

Table 2

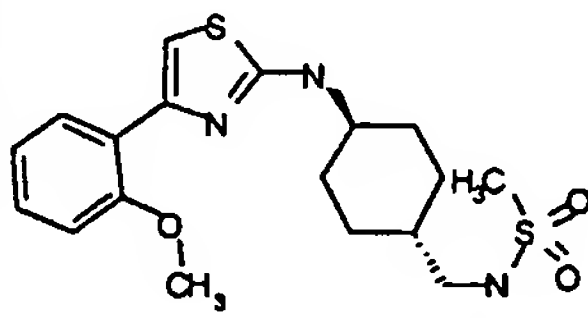
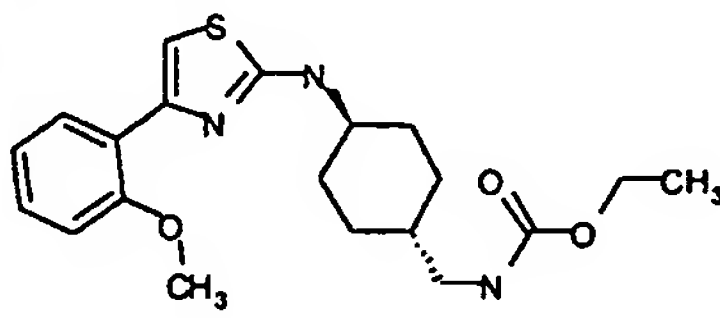
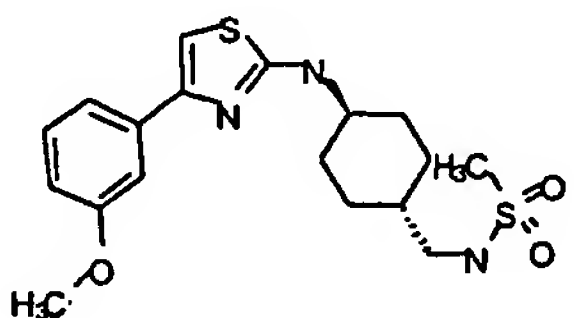
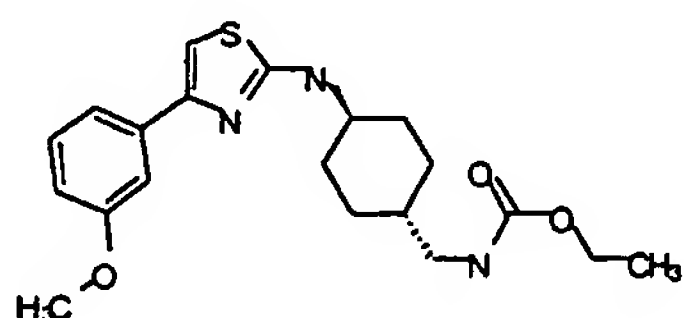
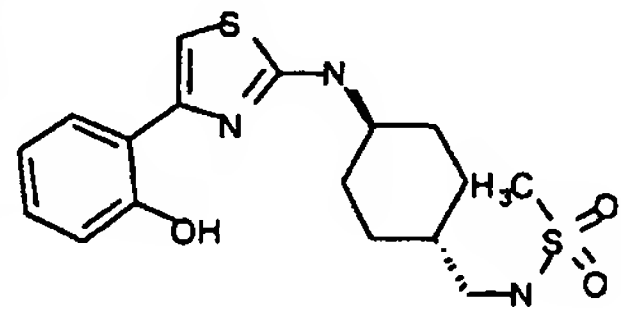
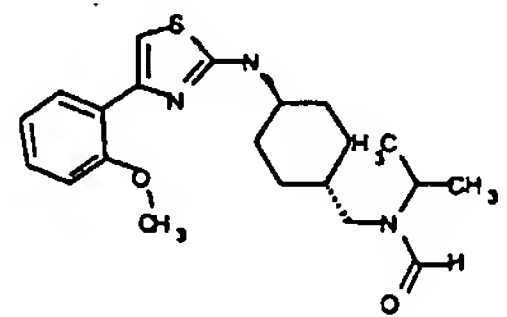
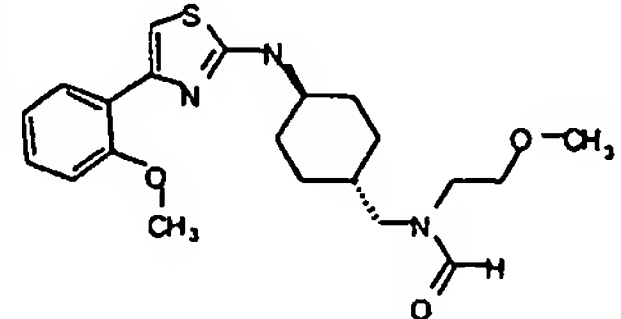
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
91		12.3	
92		912	
93		150	
94		240	
95		106	
96		56	
97		335	

Table 2 continued

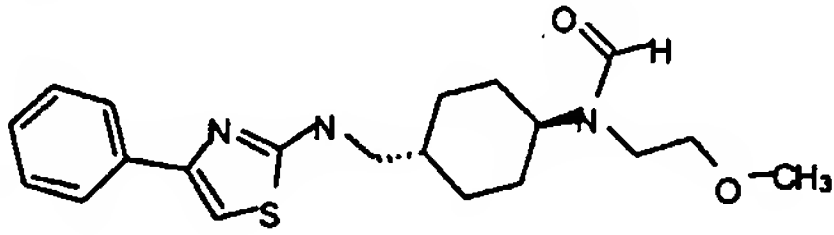
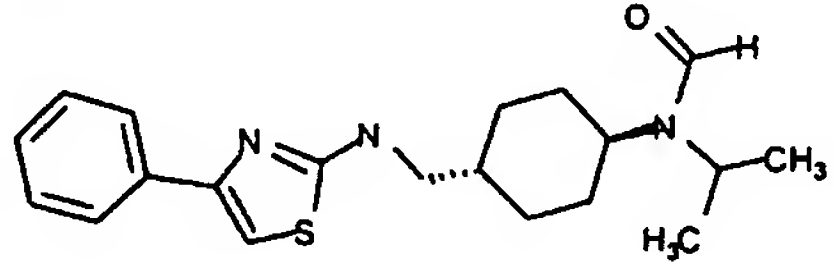
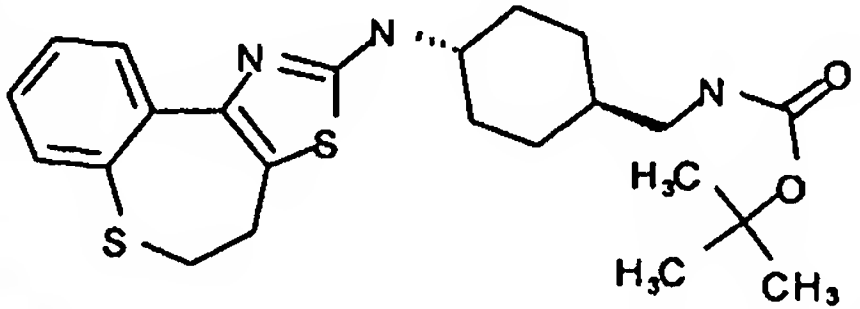
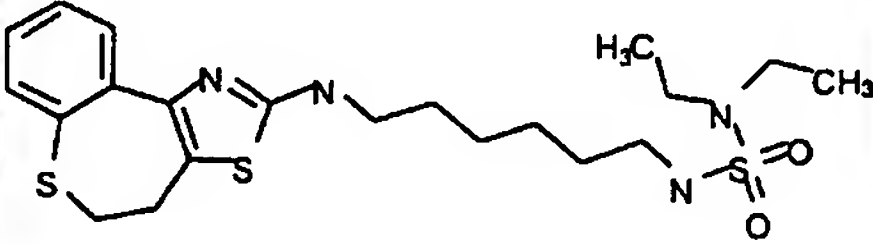
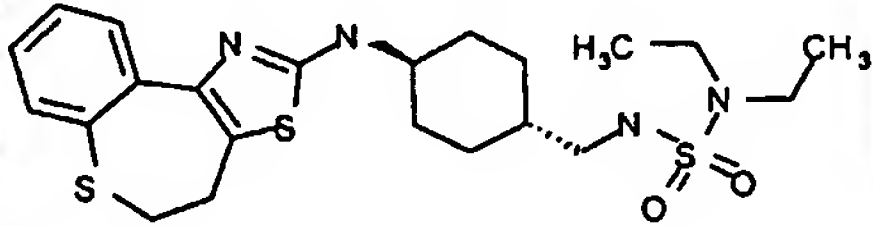
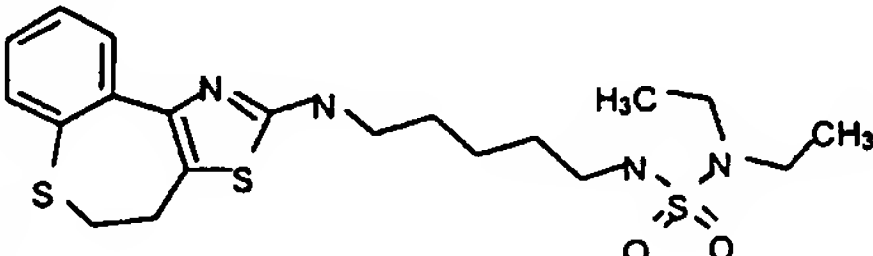
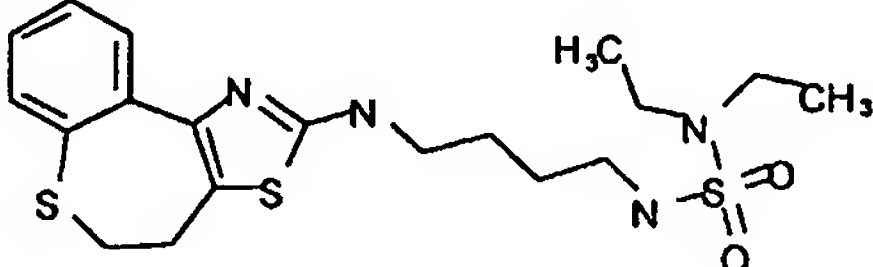
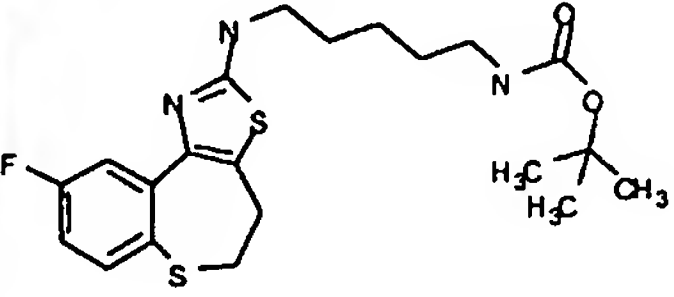
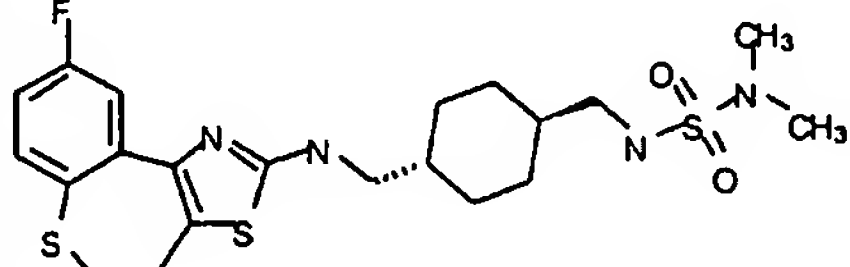
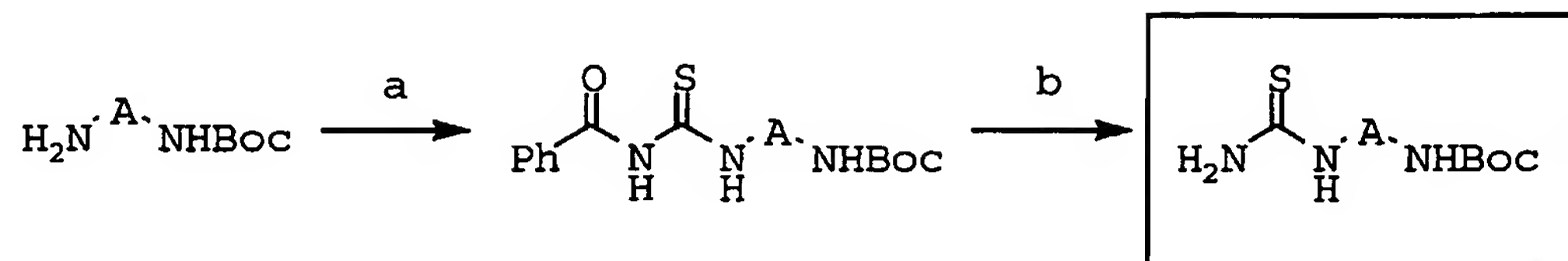
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1, 2, 4
98		125	
99		45	

Table 3

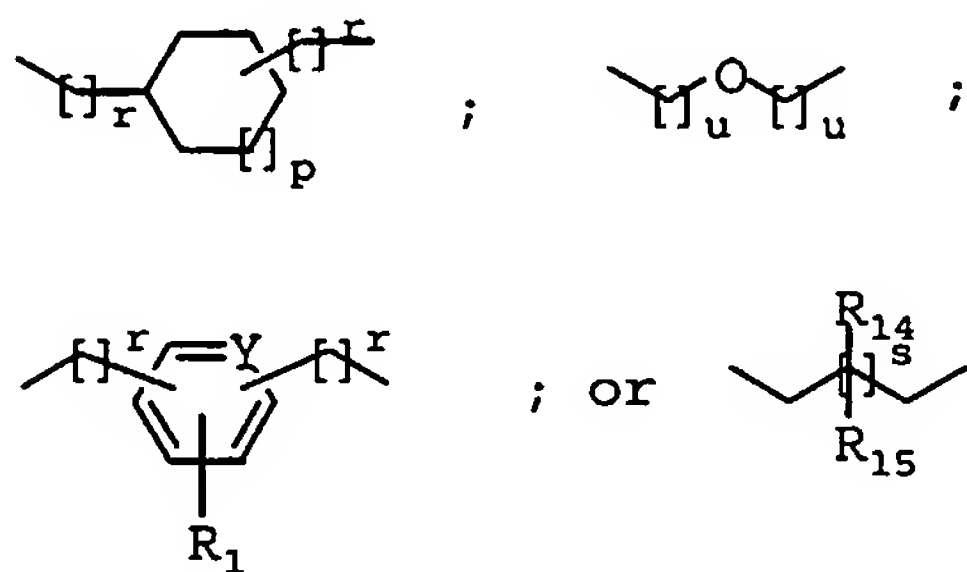
EXAMPLE	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
100		24	
101		5.9	
102		5.2	>10000
103		3.7	>10000
104		3.2	>10000
105		91	>10000
106		2.6	

Scheme 1A. Synthesis of Thioureas

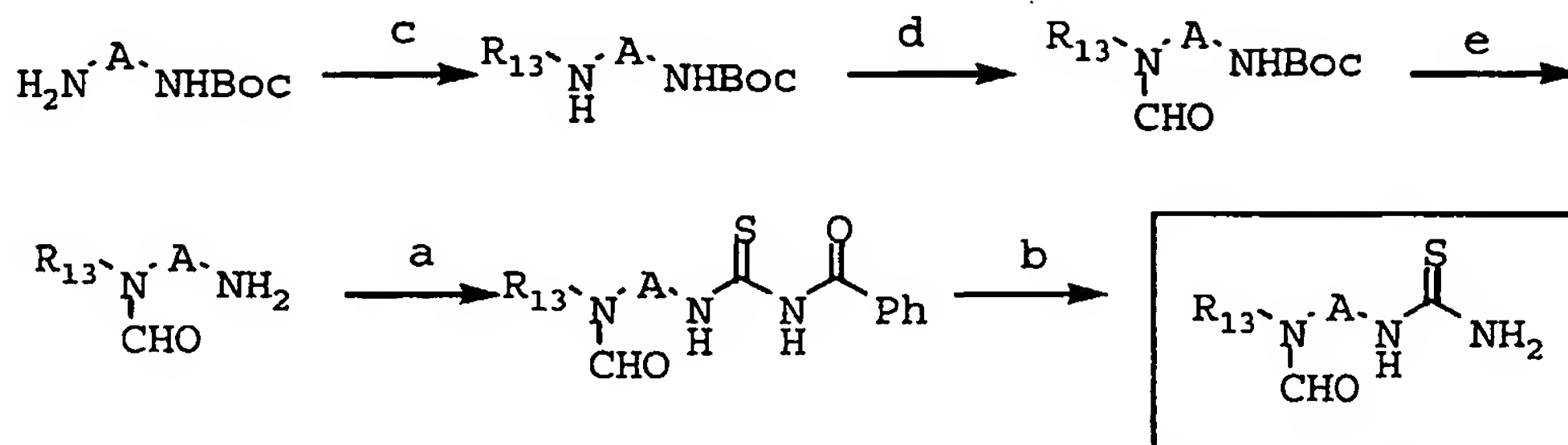


- a. benzoylisothiocyanate
b. K_2CO_3 , MeOH

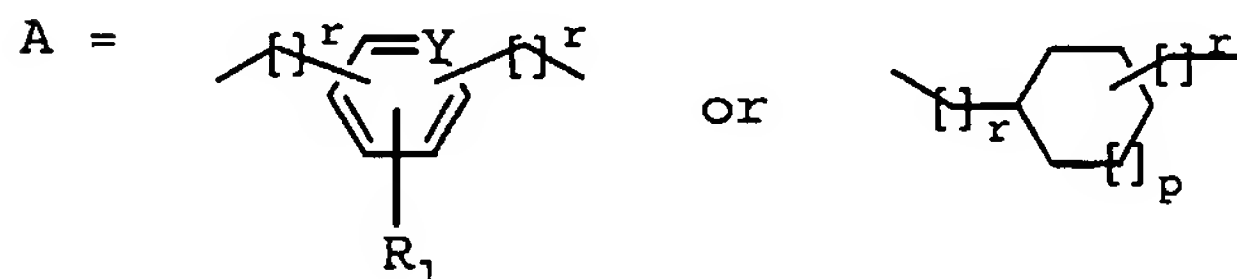
A =



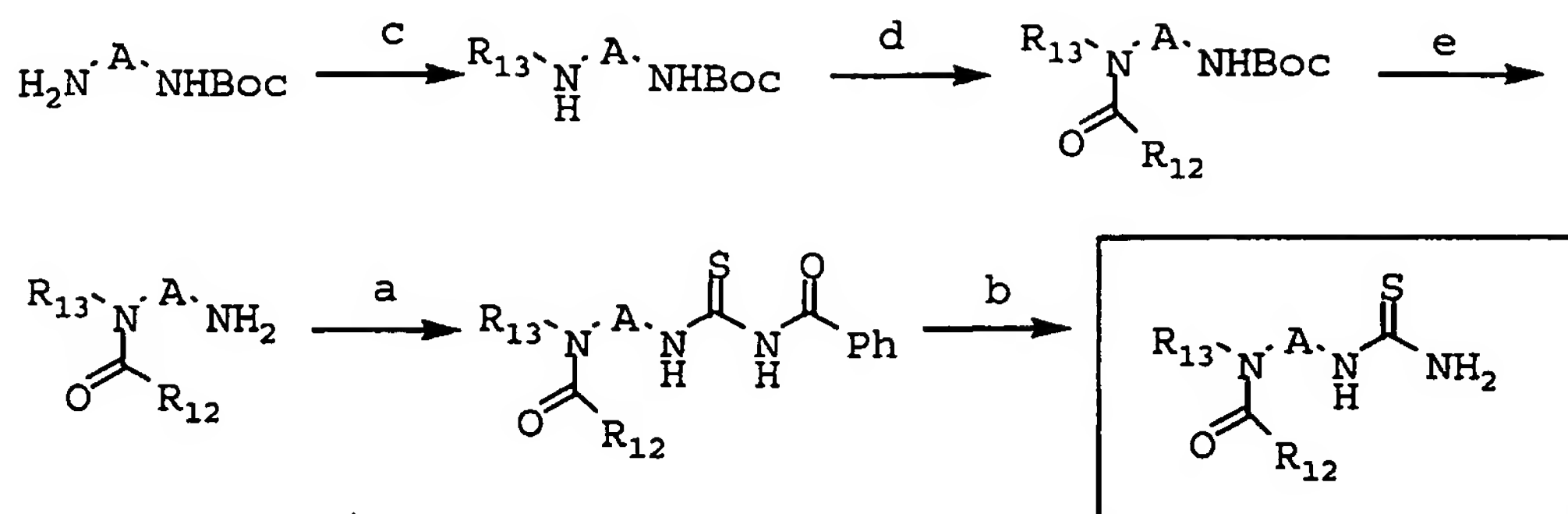
Scheme 1B. Synthesis of Thioureas



- a. Benzoylisothiocyanate
b. K_2CO_3 , MeOH
c. alkyl halide or acyl halide followed by borane reduction
d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde
e. HCl or TFA



Scheme 1C. Synthesis of Thioureas



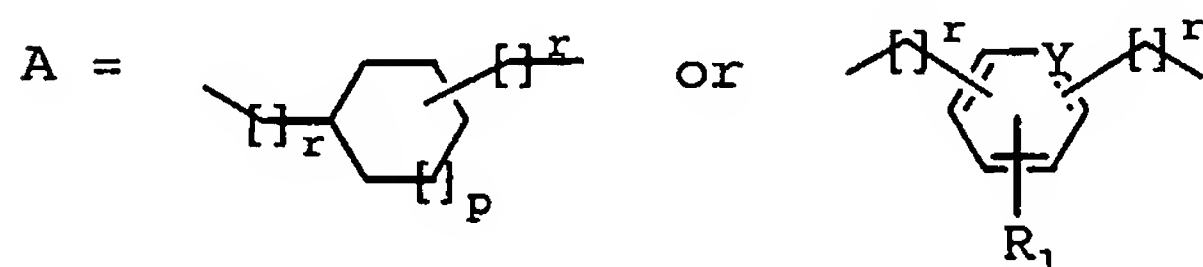
a. Benzoylisothiocyanate

b. K_2CO_3 , MeOH

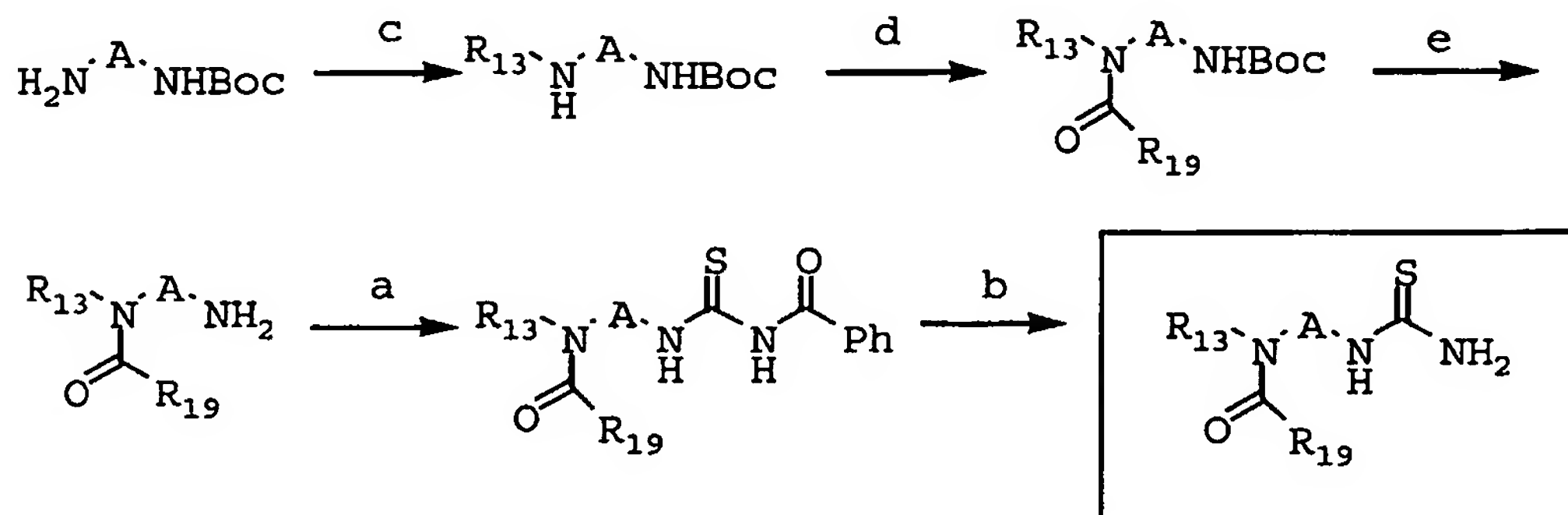
c. alkyl halide or acyl halide followed by borane reduction

d. $R_{12}COCl$

e. HCl or TFA



Scheme 1D. Synthesis of Thioureas



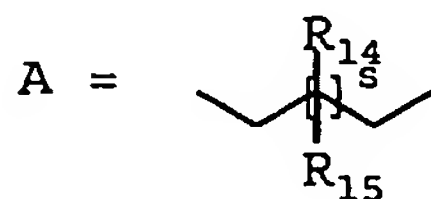
a. benzoylisothiocyanate

b. K_2CO_3 , MeOH

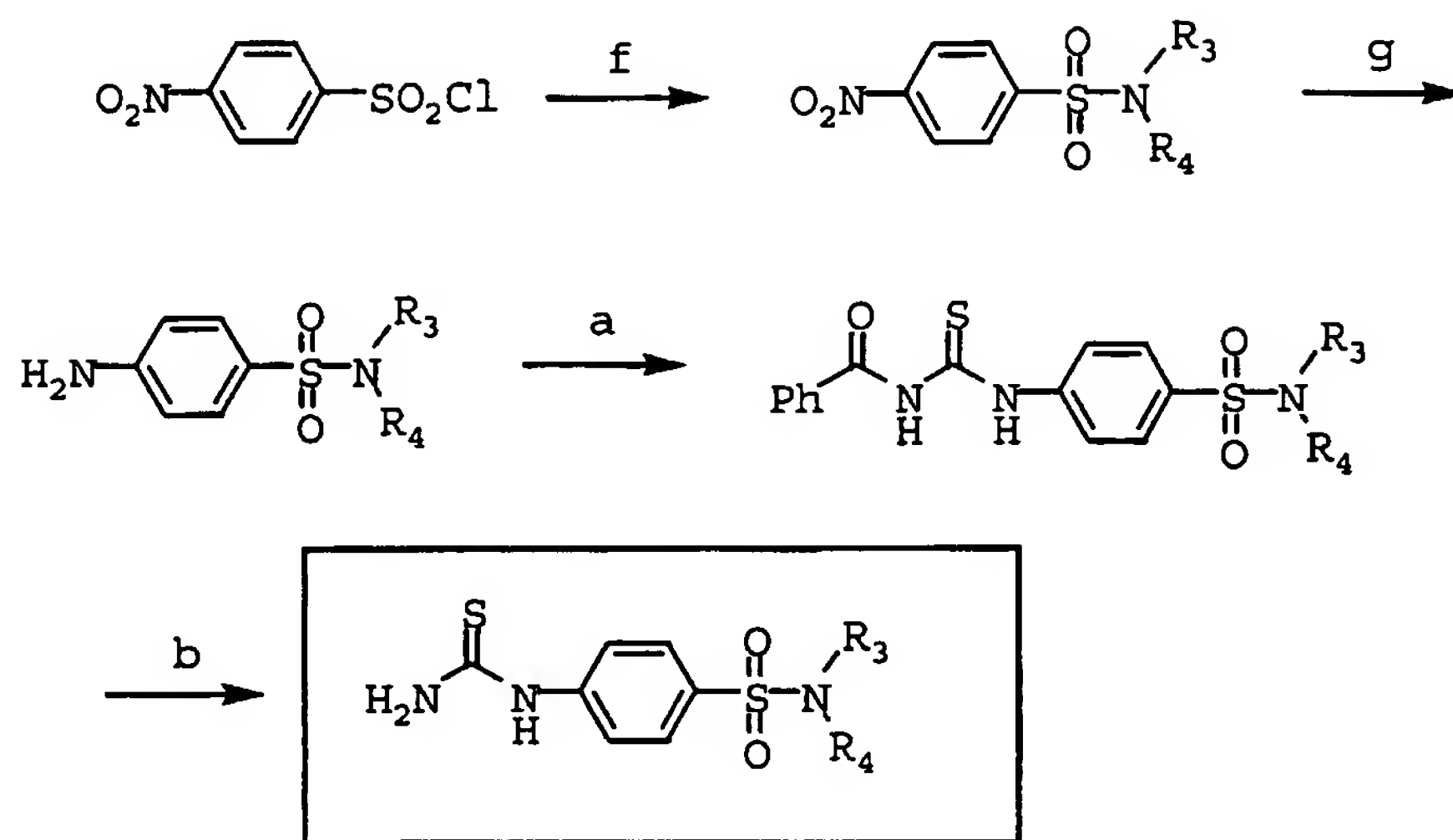
c. alkyl halide or acyl halide followed by borane reduction

d. $R_{19}COCl$

e. HCl or TFA



Scheme 1E. Synthesis of Thioureas

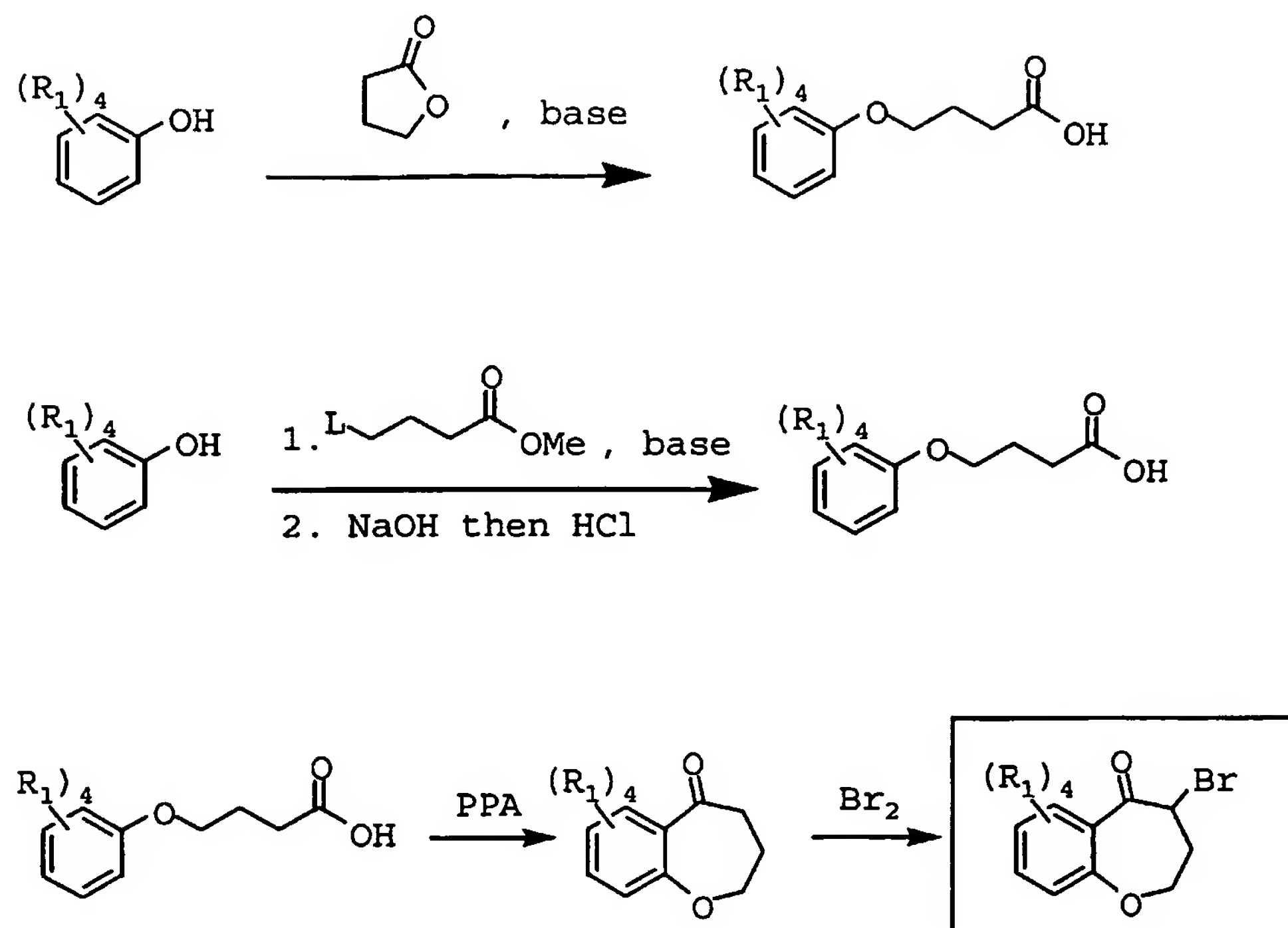


a. benzoylisothiocyanate

b. K_2CO_3 , MeOHf. HNR_3R_4

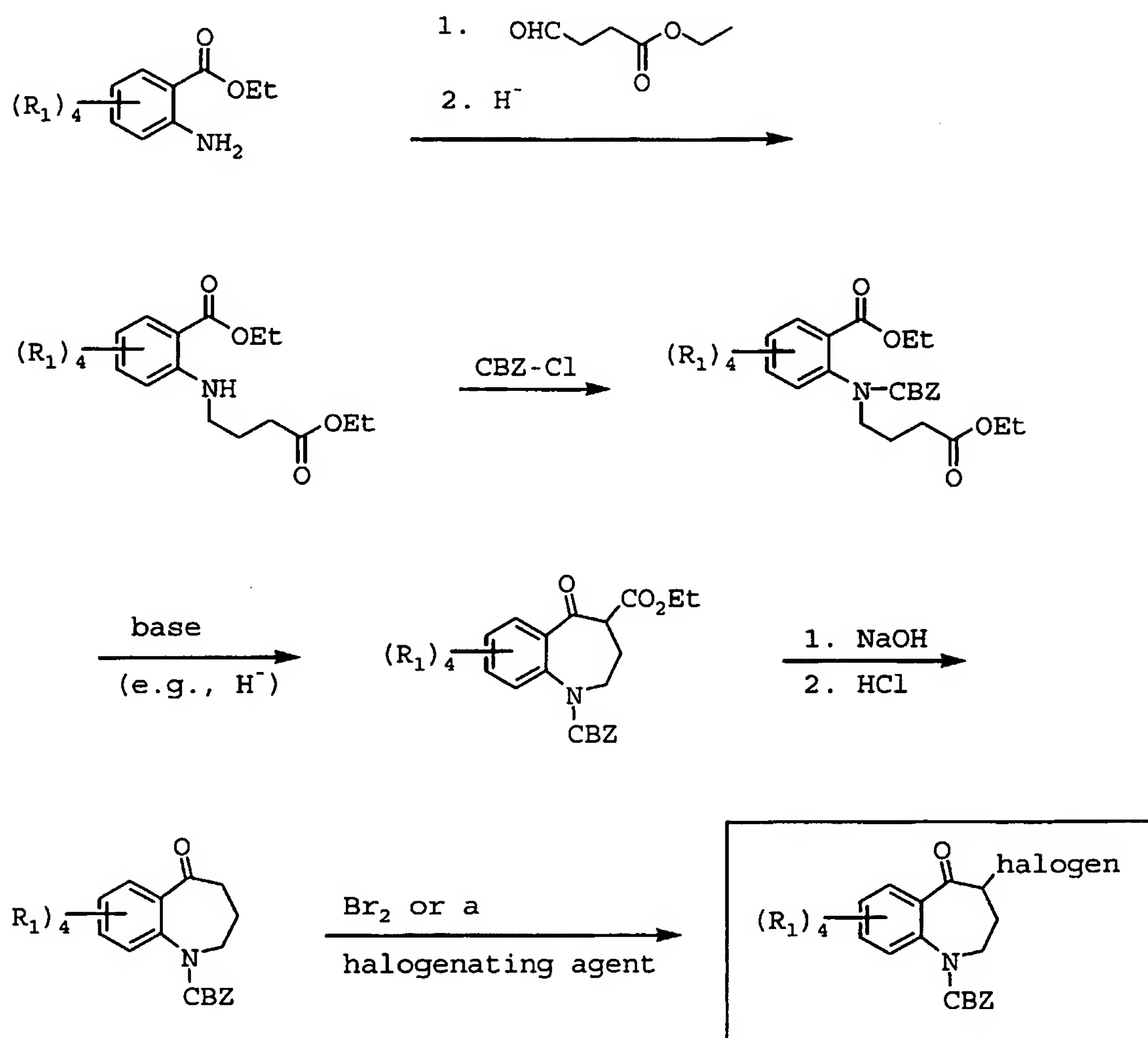
g. reduction

Scheme 2A. Synthesis of Bromoketones

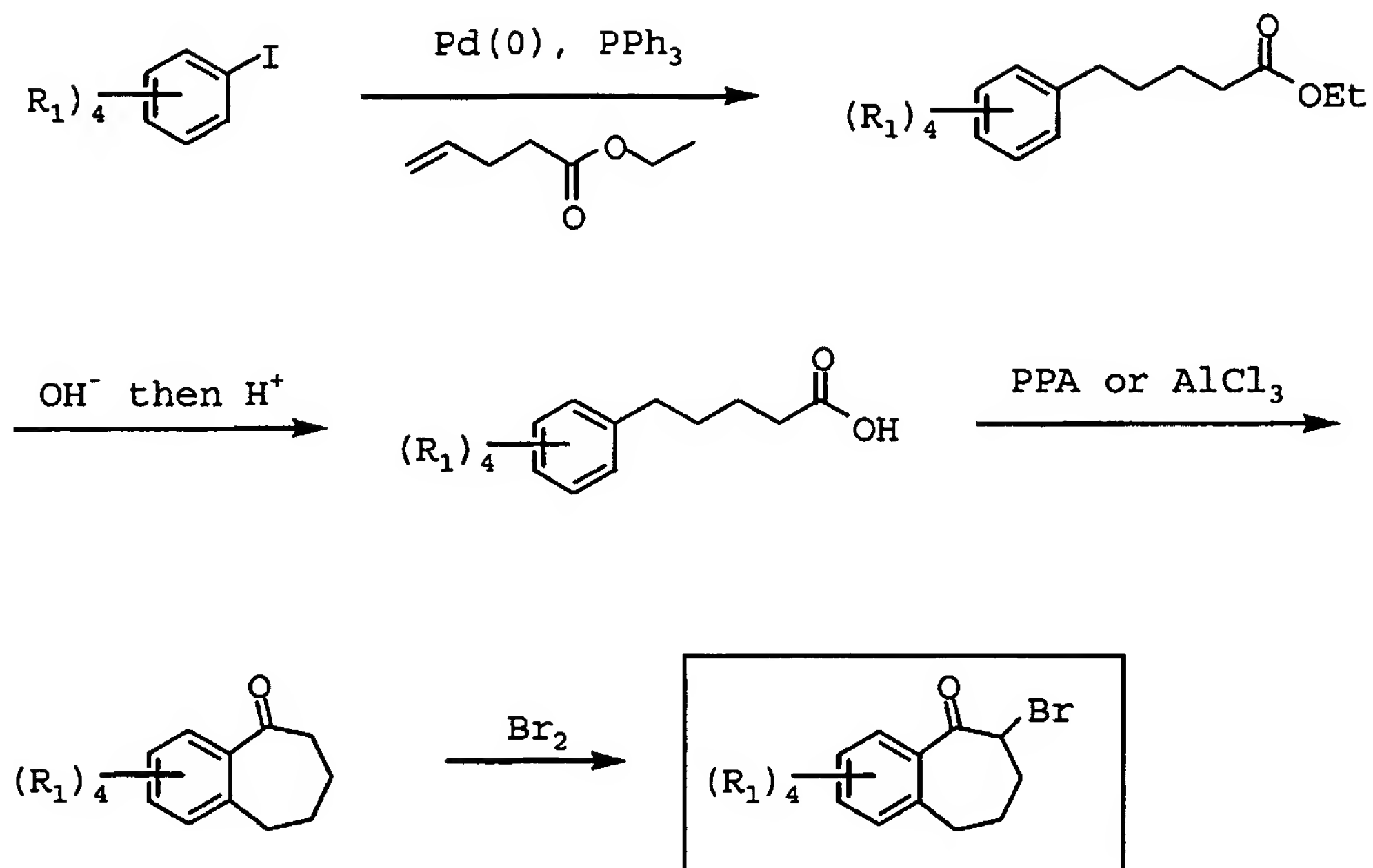


L = leaving group such as Br

Scheme 2B. Synthesis of Bromoketones

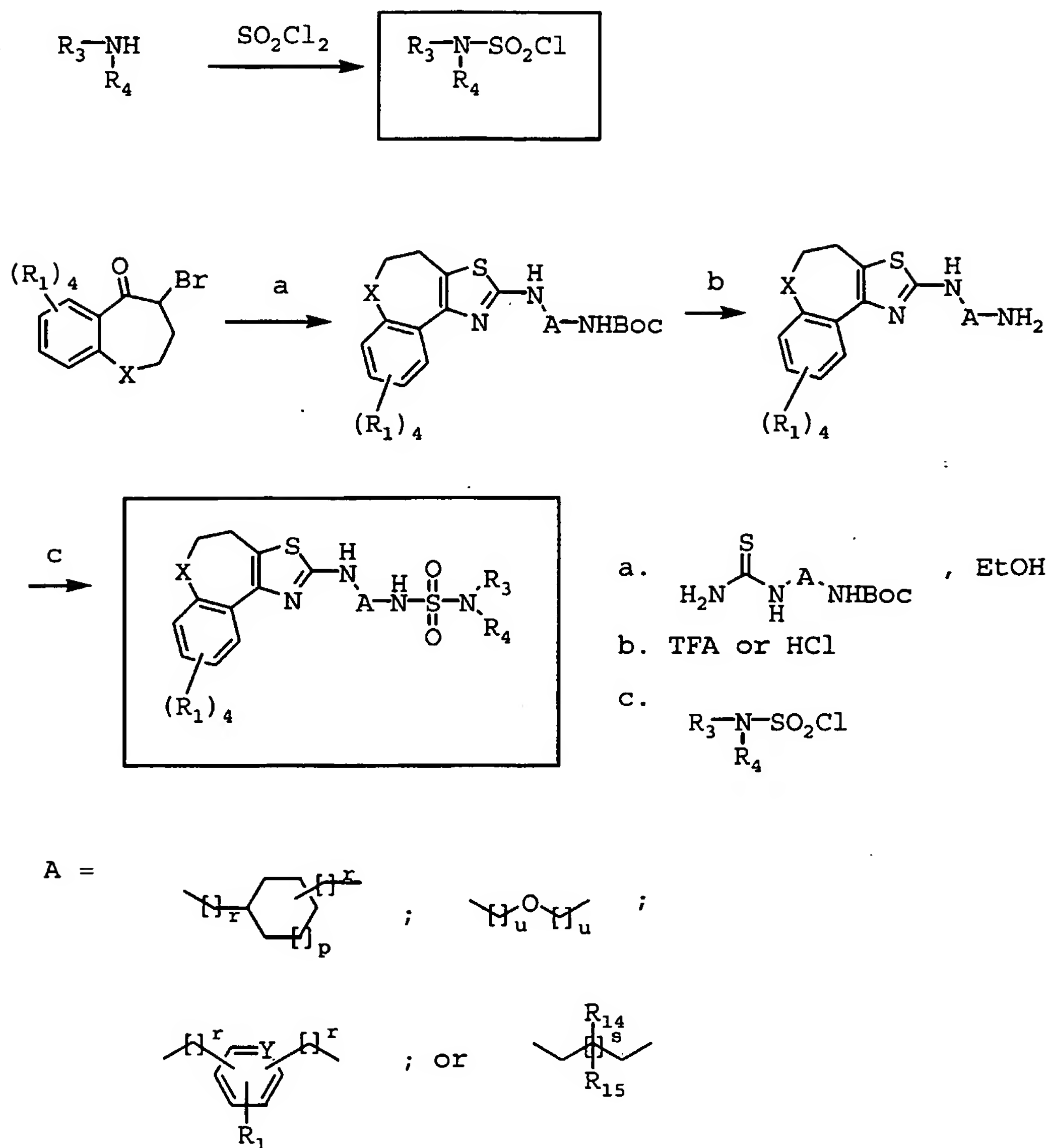


Scheme 2C. Synthesis of Bromoketones

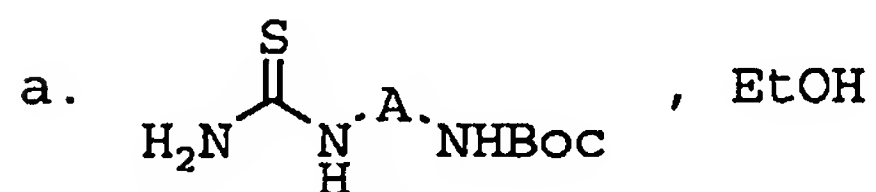
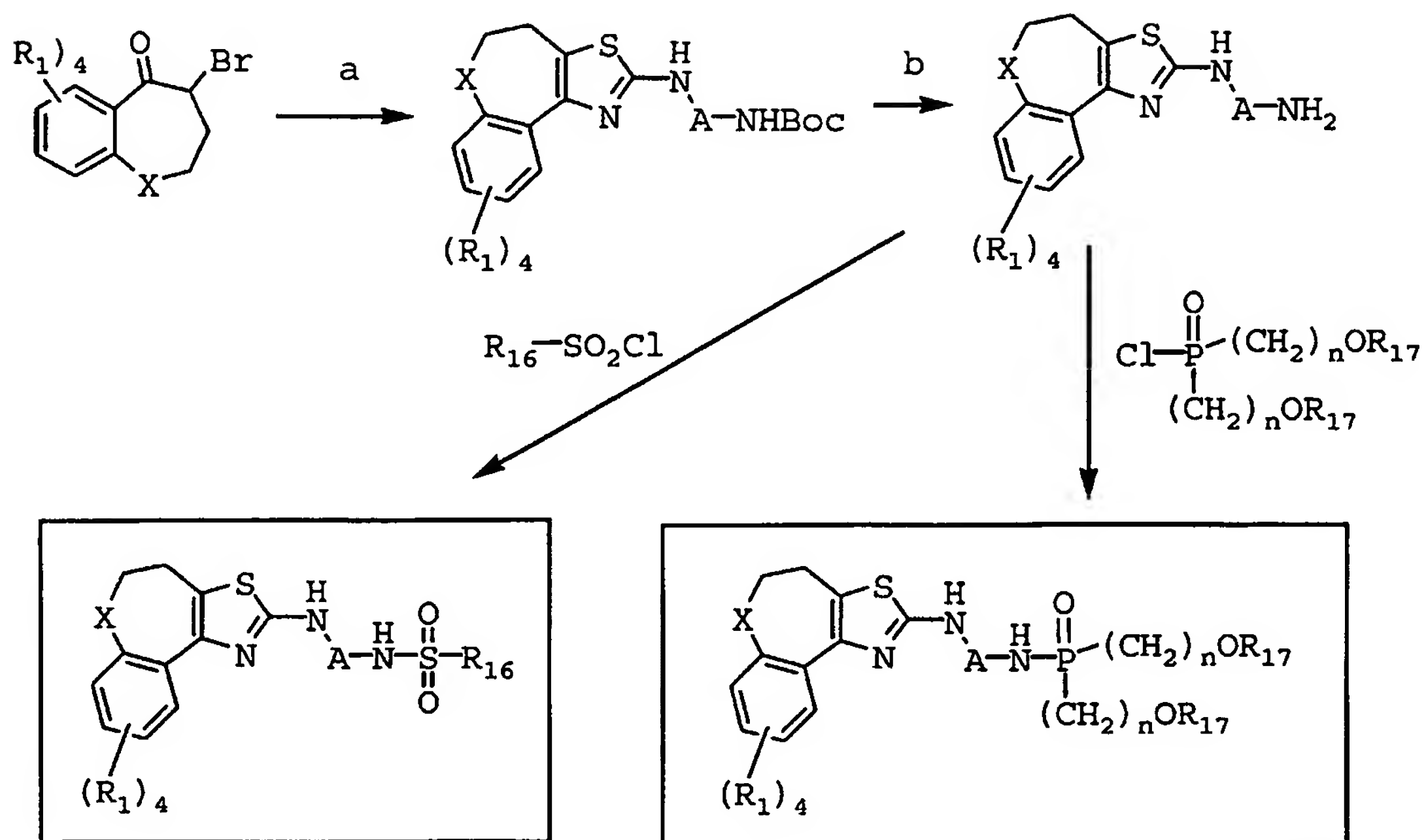


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Scheme 3A. Synthesis of the Tricycles

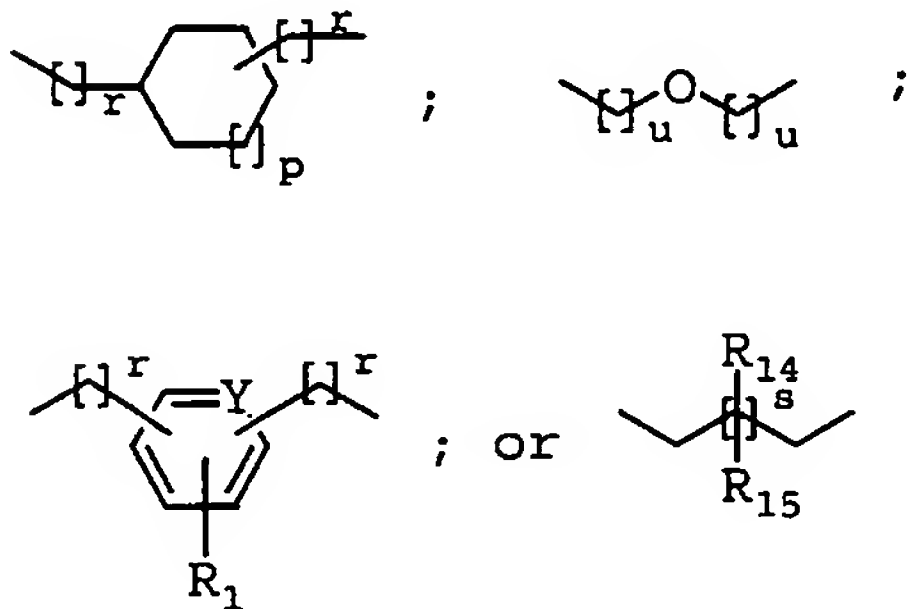


Scheme 3B. Synthesis of the Tricycles

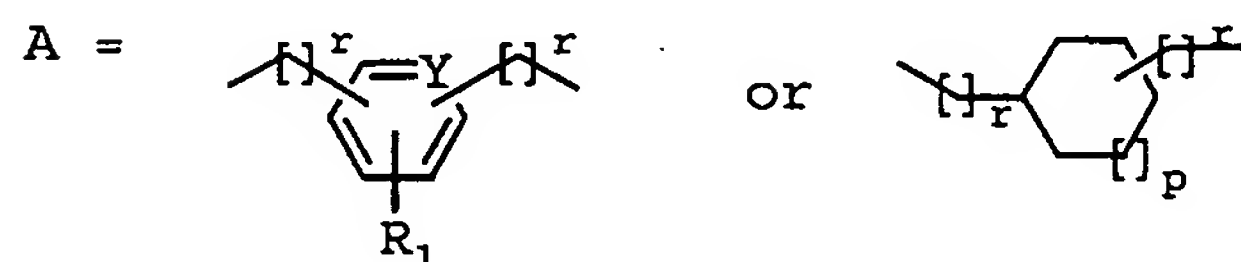
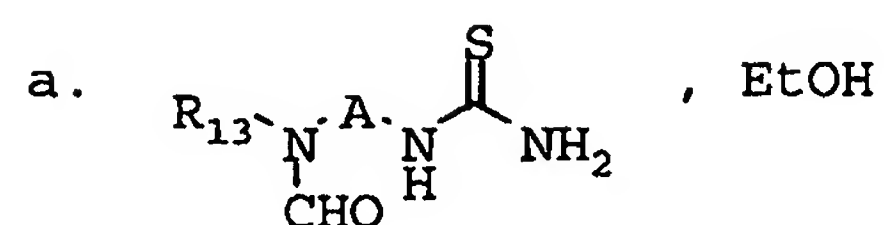
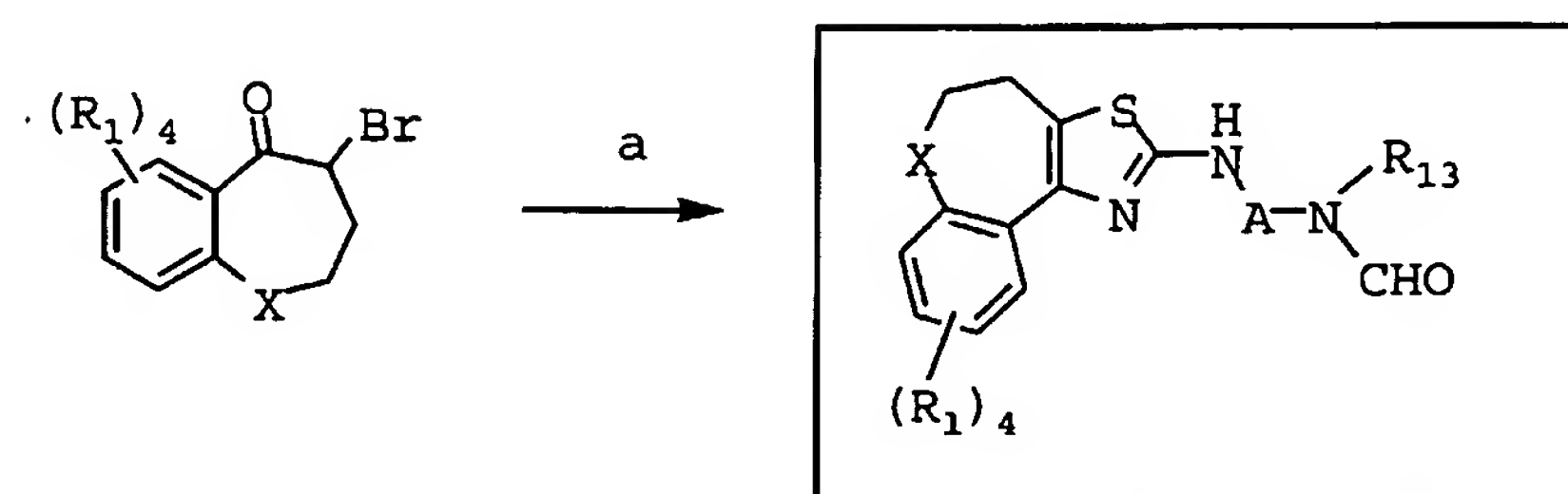


b. TFA or HCl

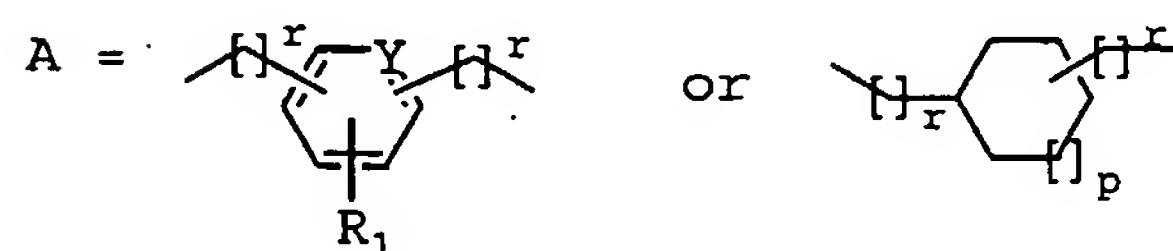
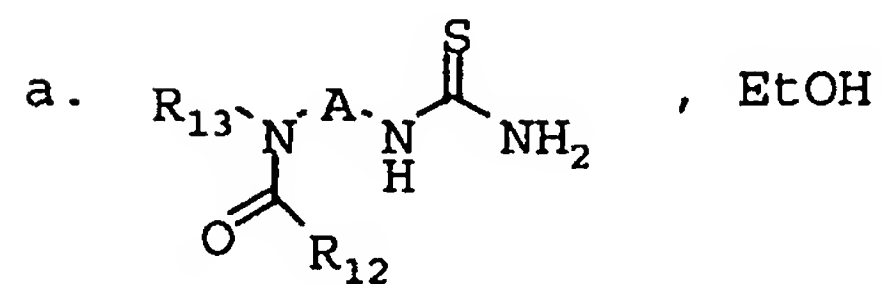
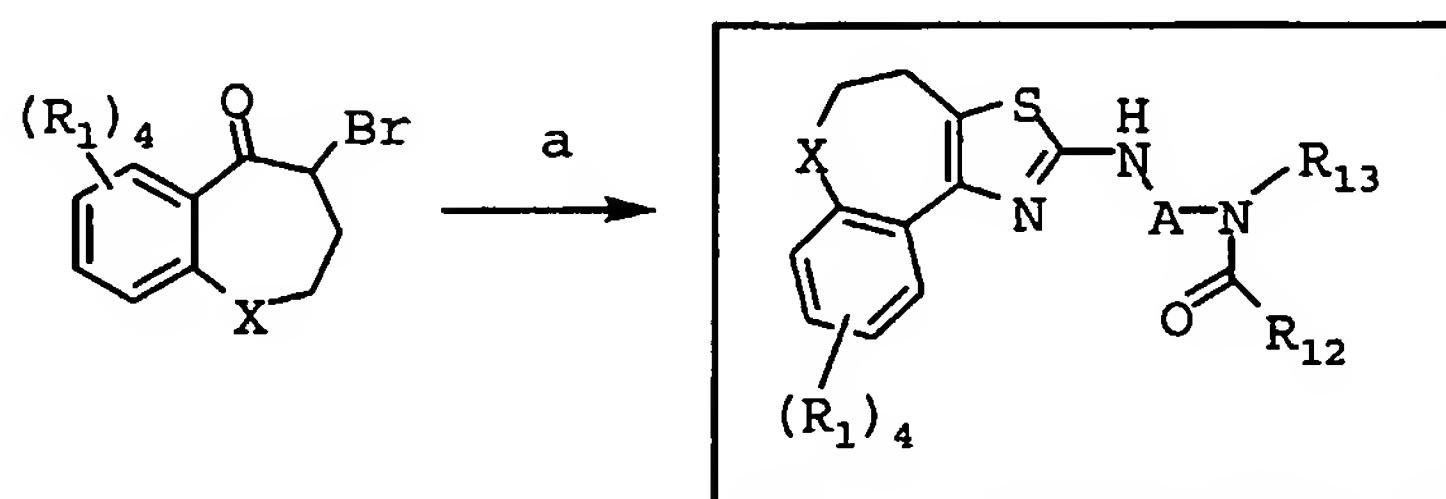
A =



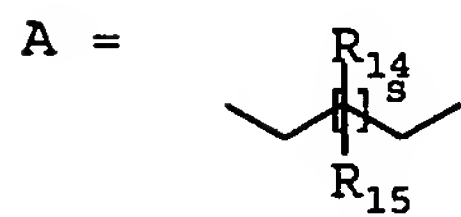
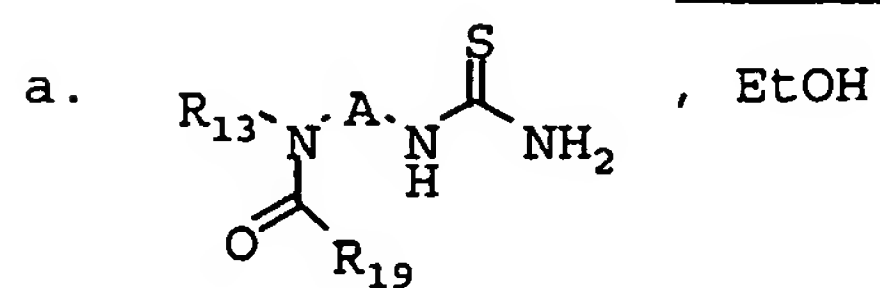
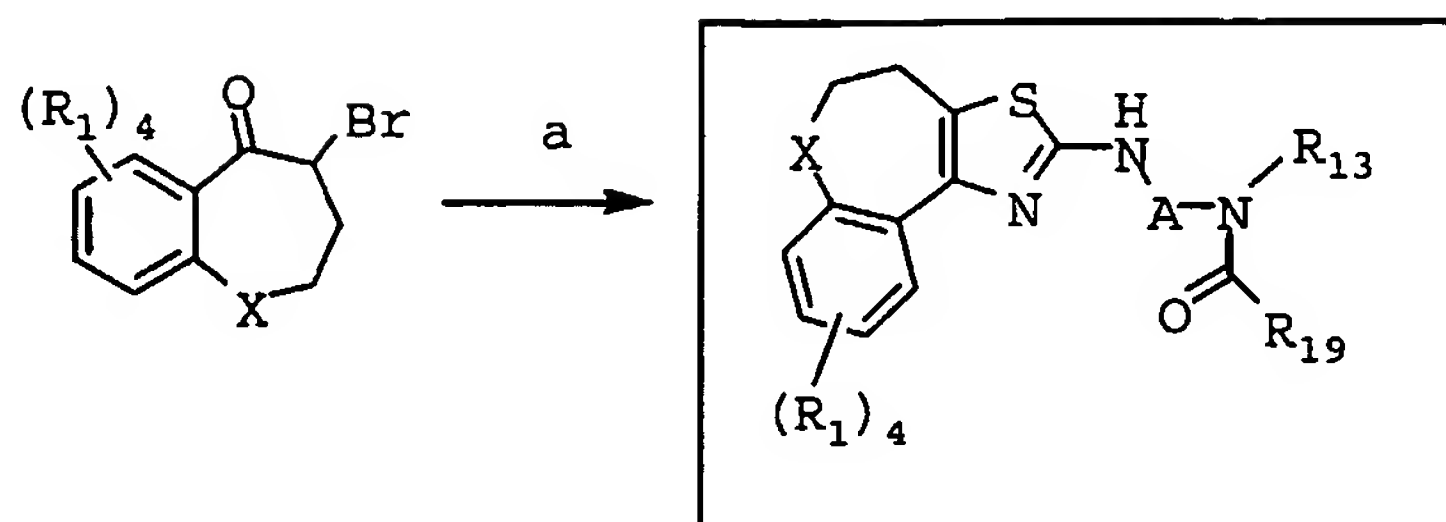
Scheme 3C. Synthesis of the Tricycles



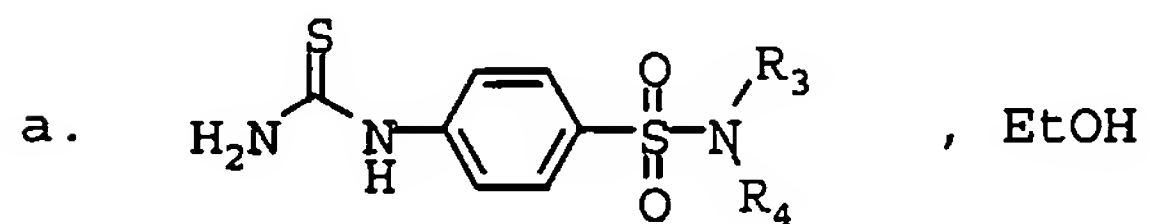
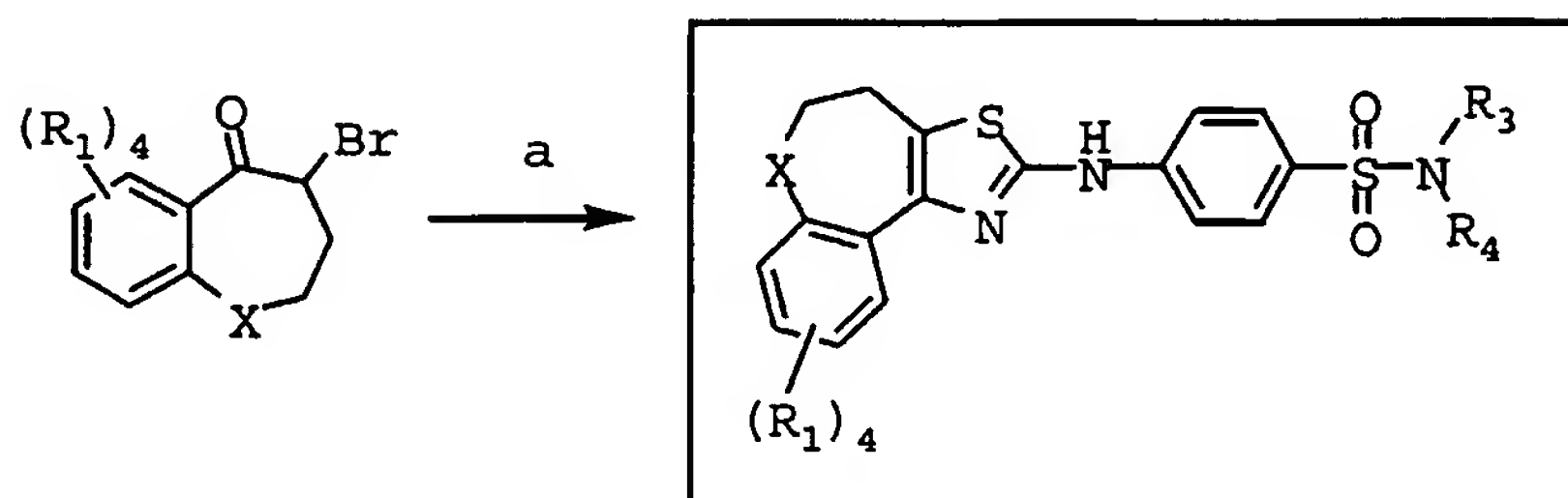
Scheme 3D. Synthesis of the Tricycles



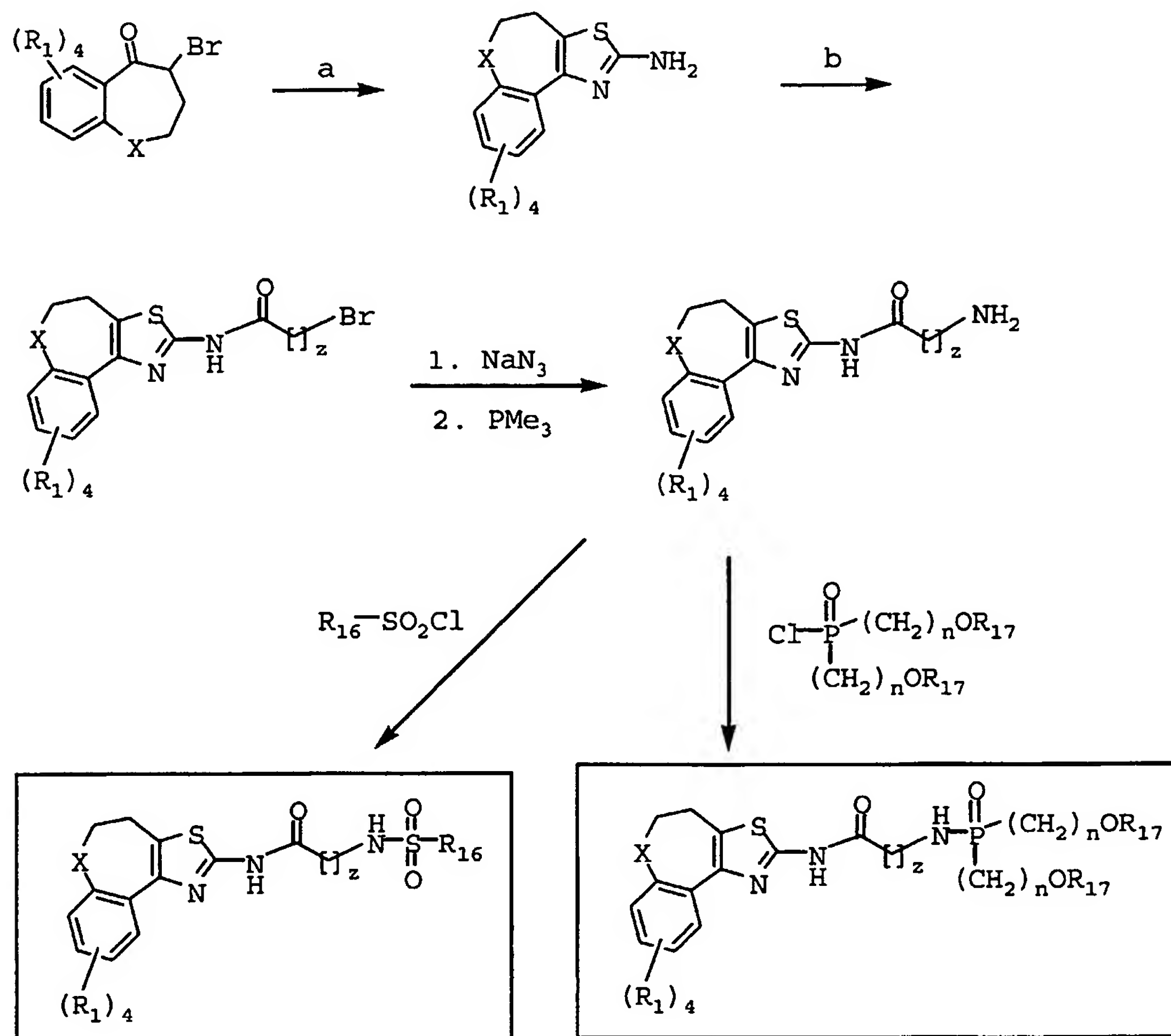
Scheme 3E. Synthesis of the Tricycles

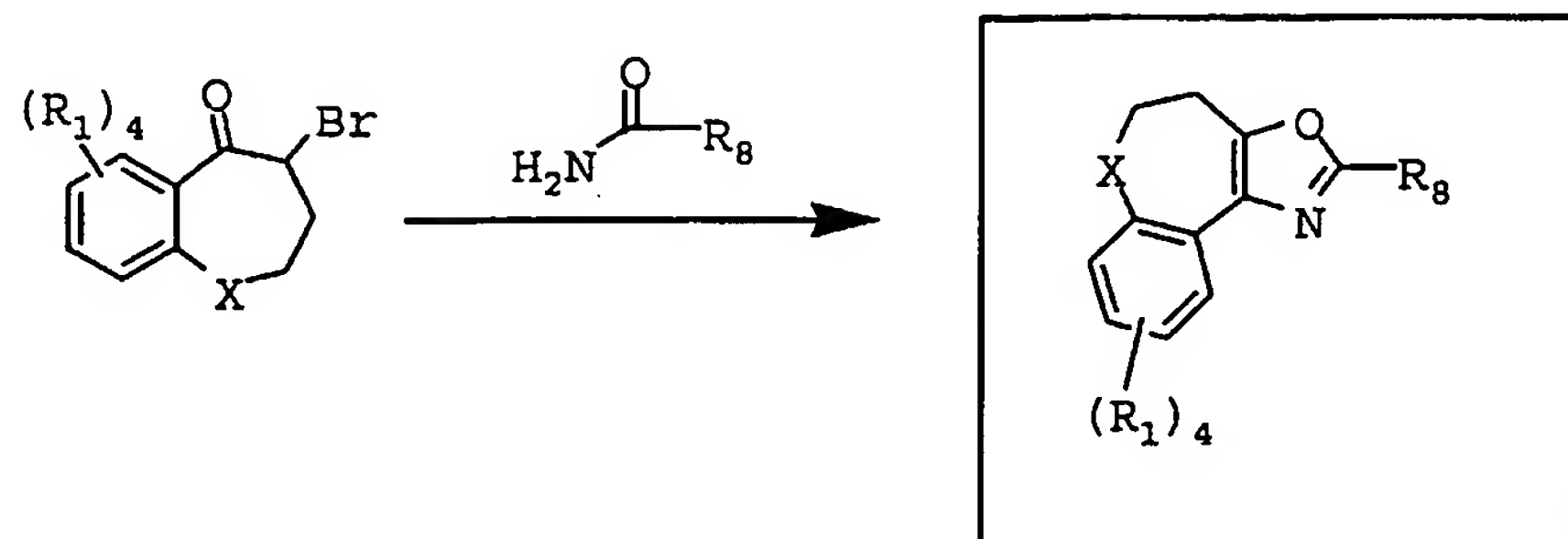
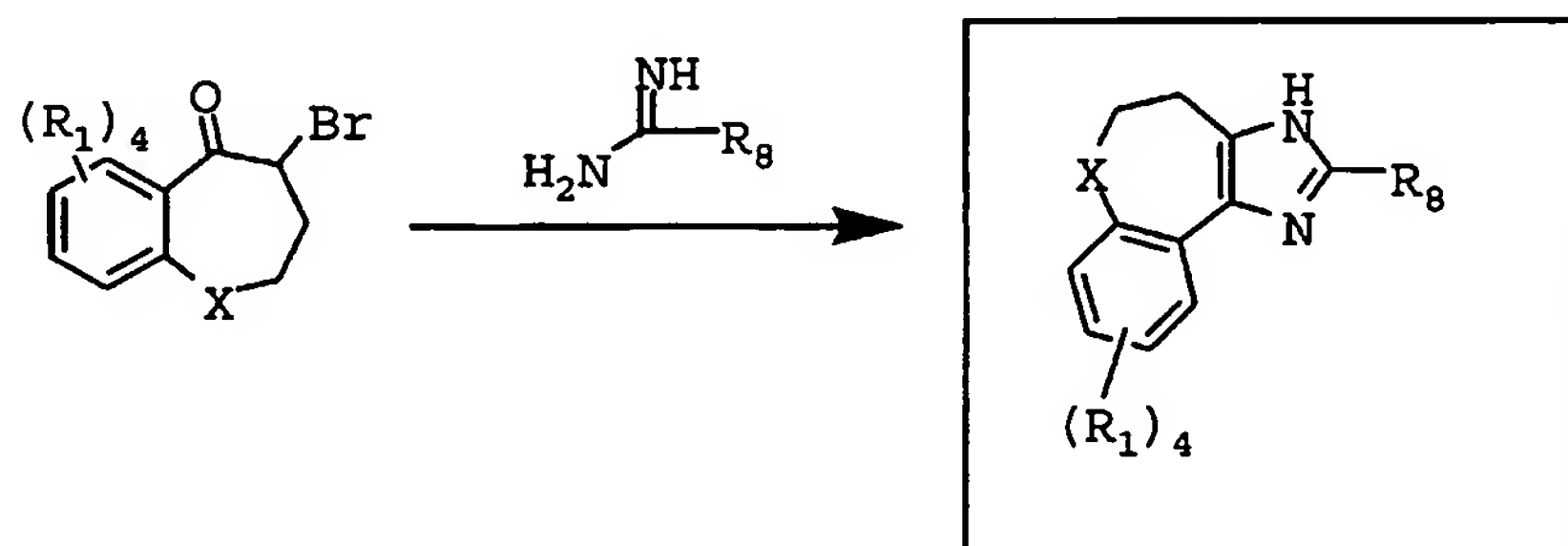


Scheme 3F. Synthesis of the Tricycles

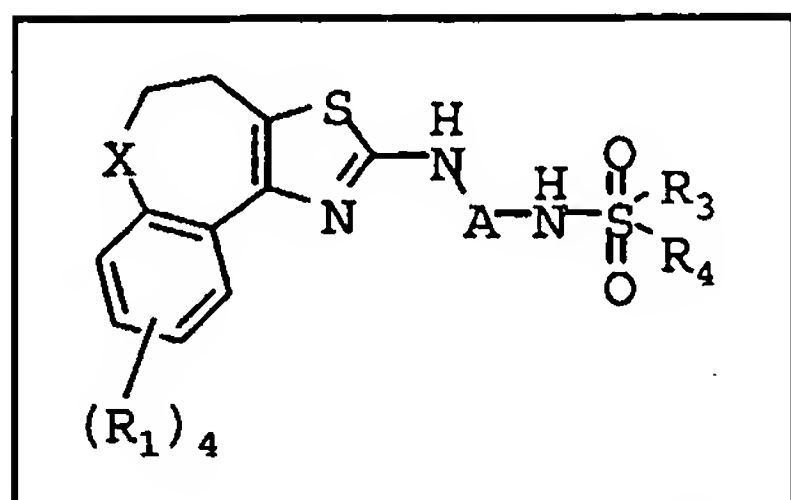
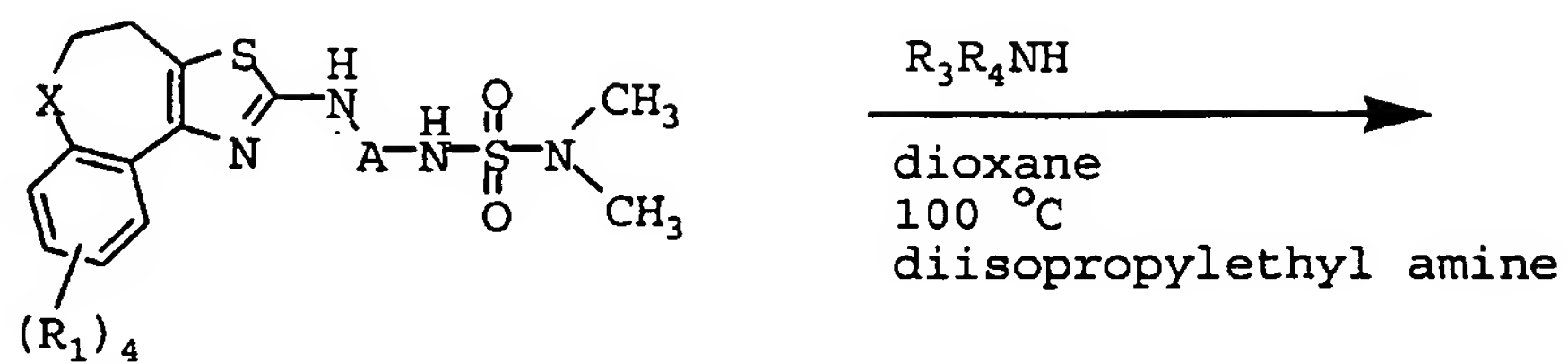


Scheme 3G. Synthesis of the Tricycles

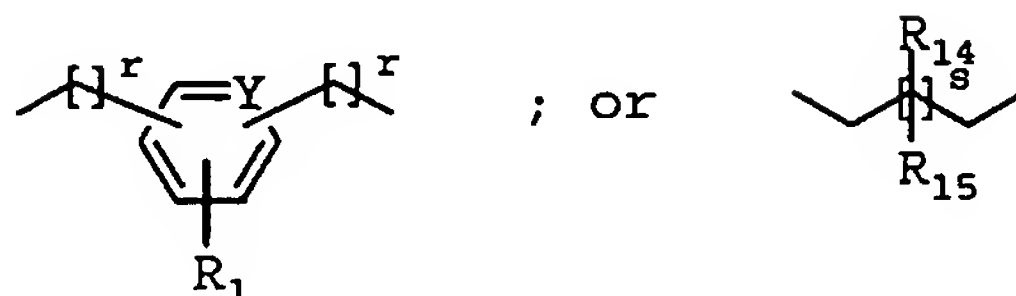
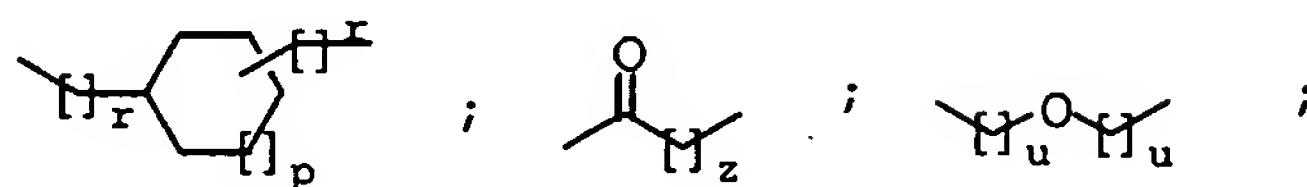


Scheme 4A. Synthesis of Tricycles**Scheme 4B. Synthesis of Tricycles**

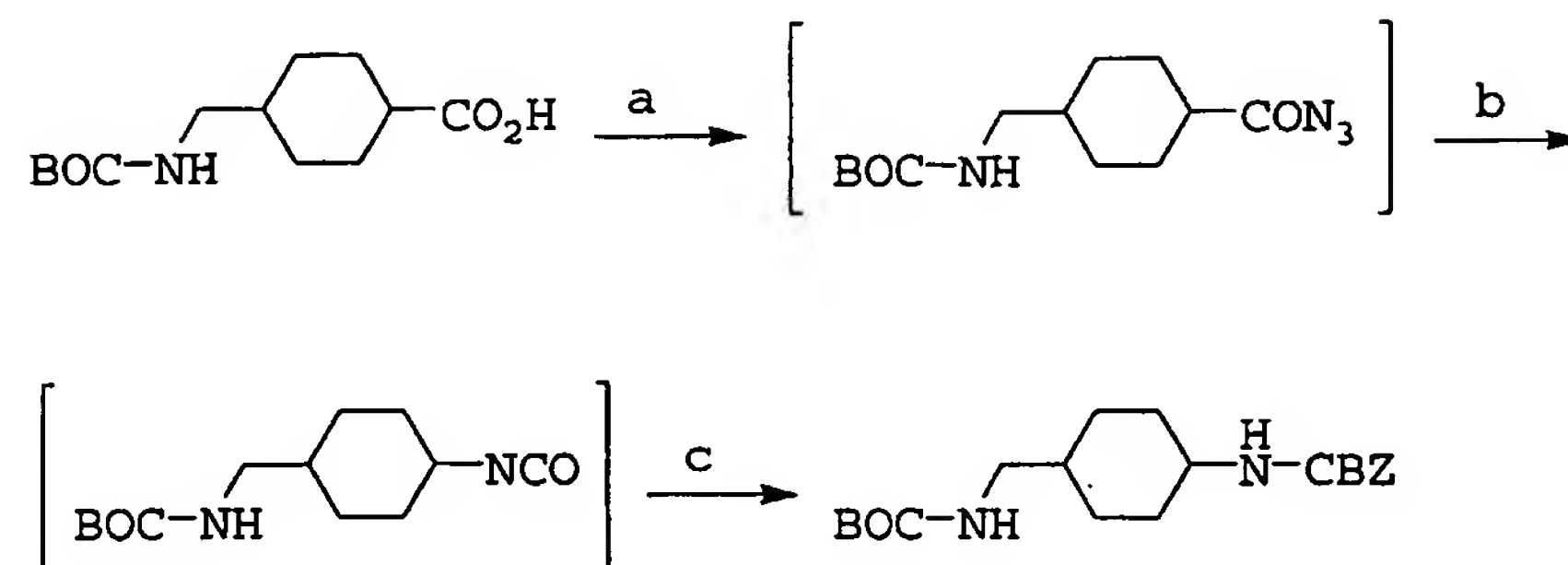
Scheme 5. Transamination of Sulfonylureas



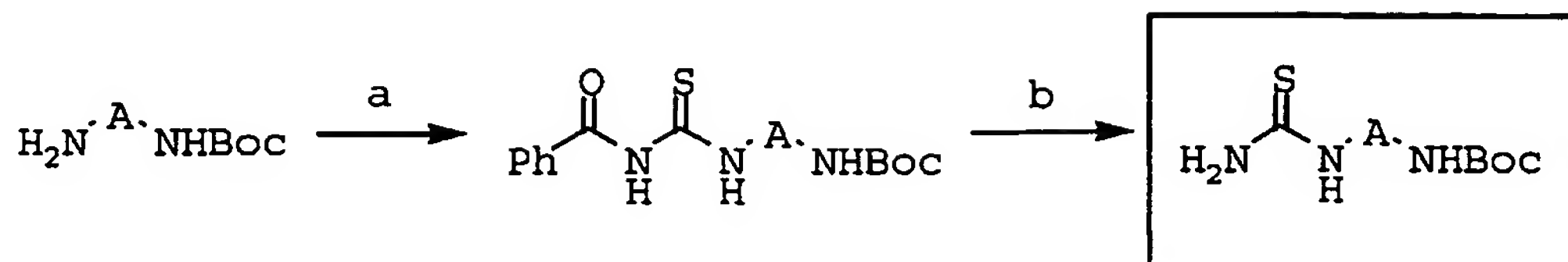
A =



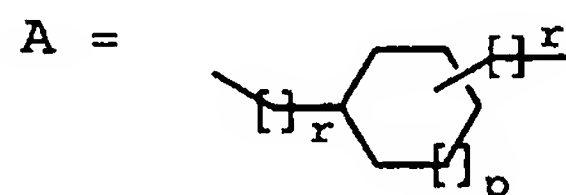
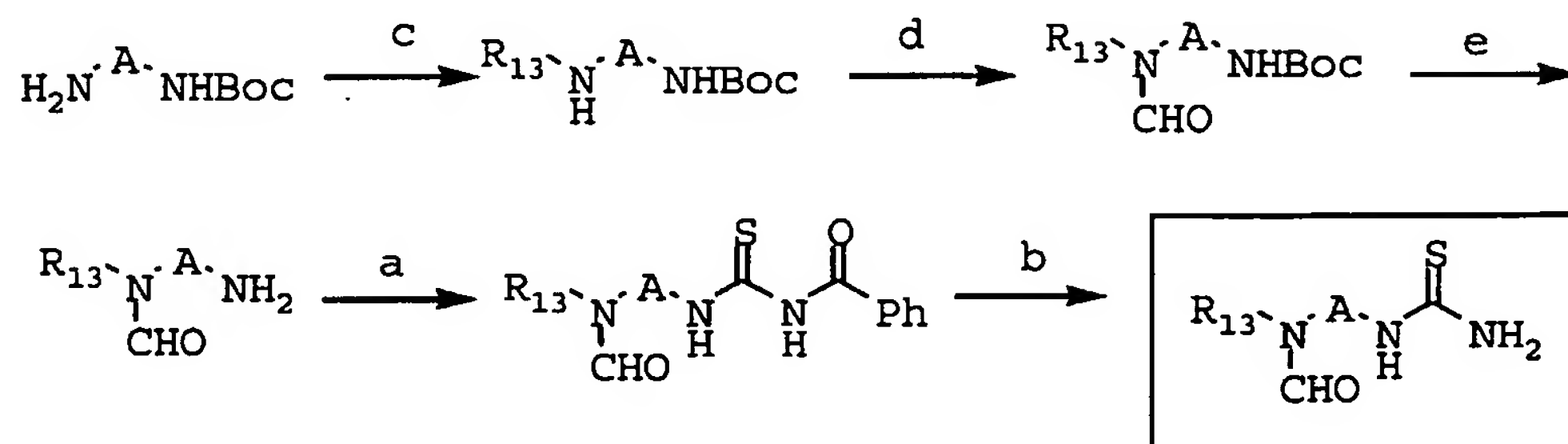
Scheme 6: Synthesis of Side Chains



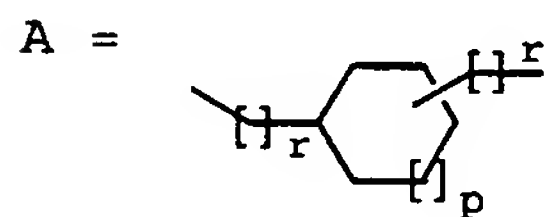
a. Diphenylphosphoryl azide, triethylamine, toluene;
b. heat; c. HOCH_2Ph

Scheme 7A. Synthesis of Thioureas

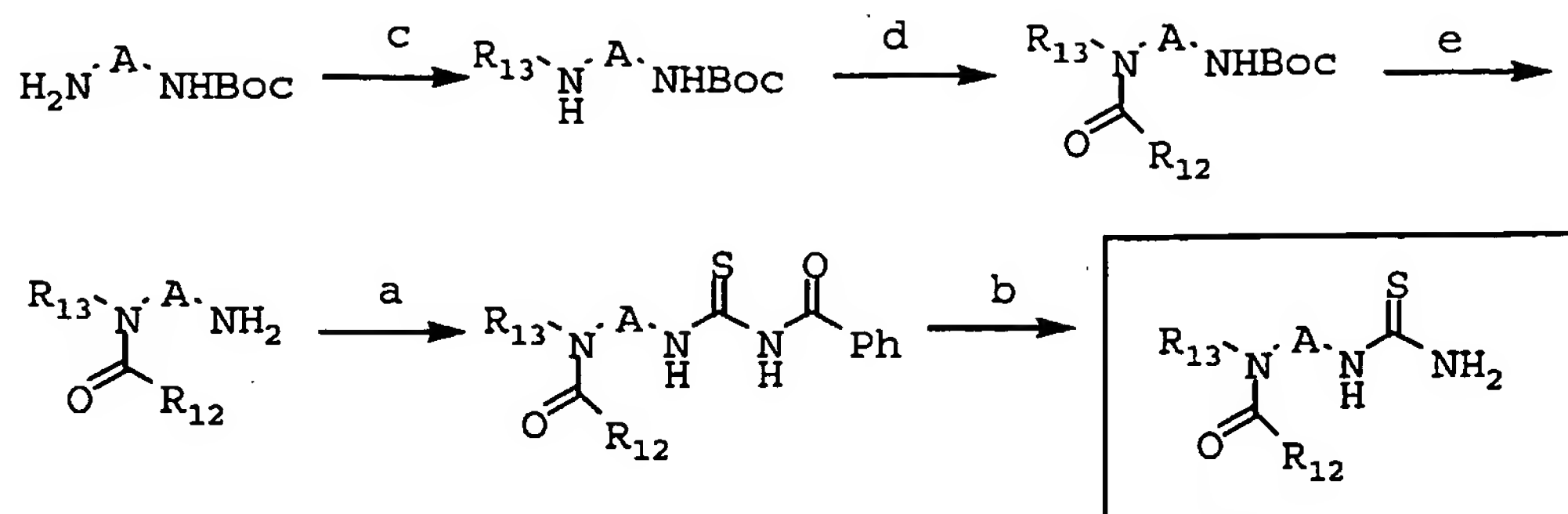
- a. benzoylisothiocyanate
b. K_2CO_3 , MeOH

**Scheme 7B. Synthesis of Thioureas**

- a. Benzoylisothiocyanate
b. K_2CO_3 , MeOH
c. alkyl halide or acyl halide followed by borane reduction
d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde
e. HCl or TFA



Scheme 7C. Synthesis of Thioureas



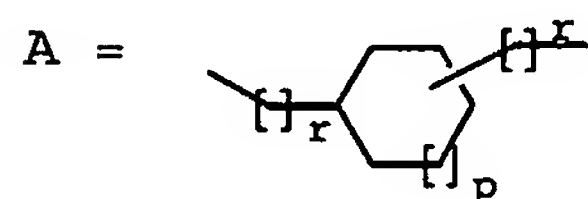
a. Benzoylisothiocyanate

b. K_2CO_3 , MeOH

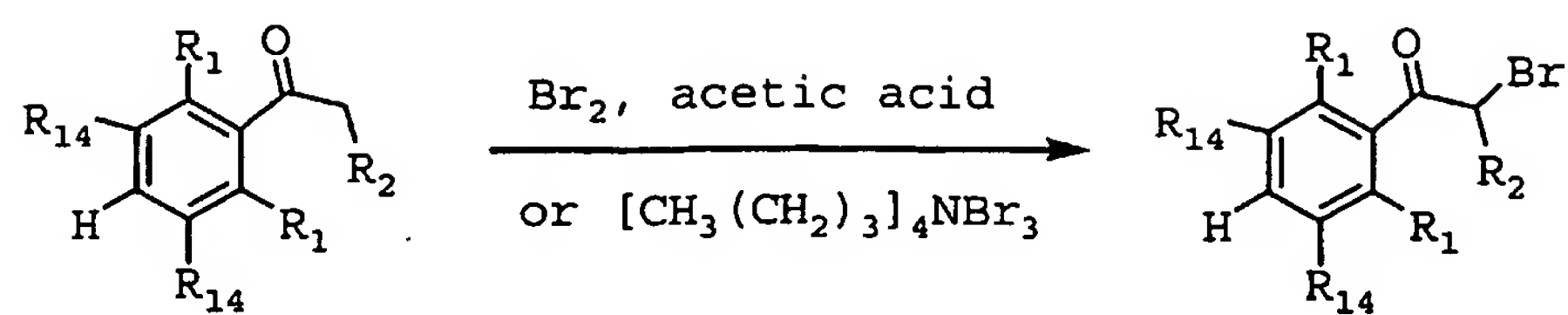
c. alkyl halide or acyl halide followed by borane reduction

d. R_{12}COCl

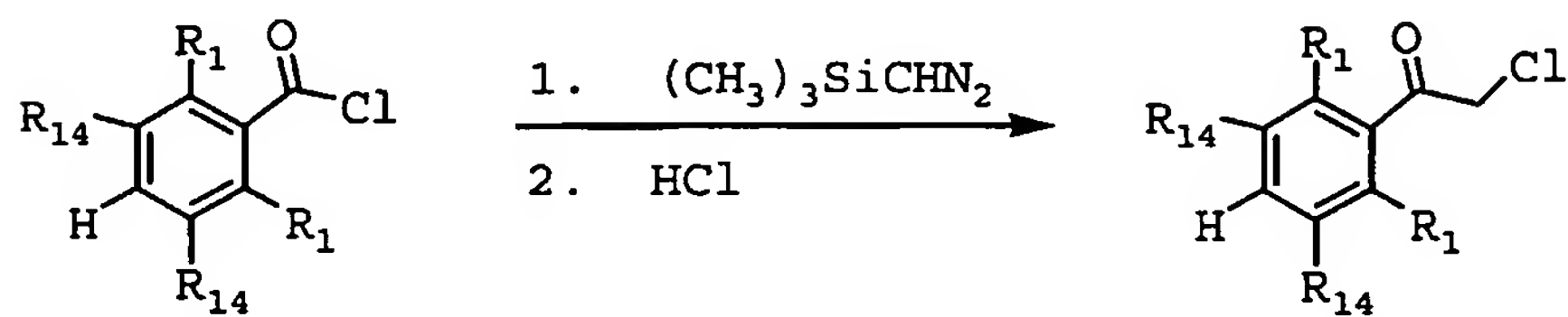
e. HCl or TFA



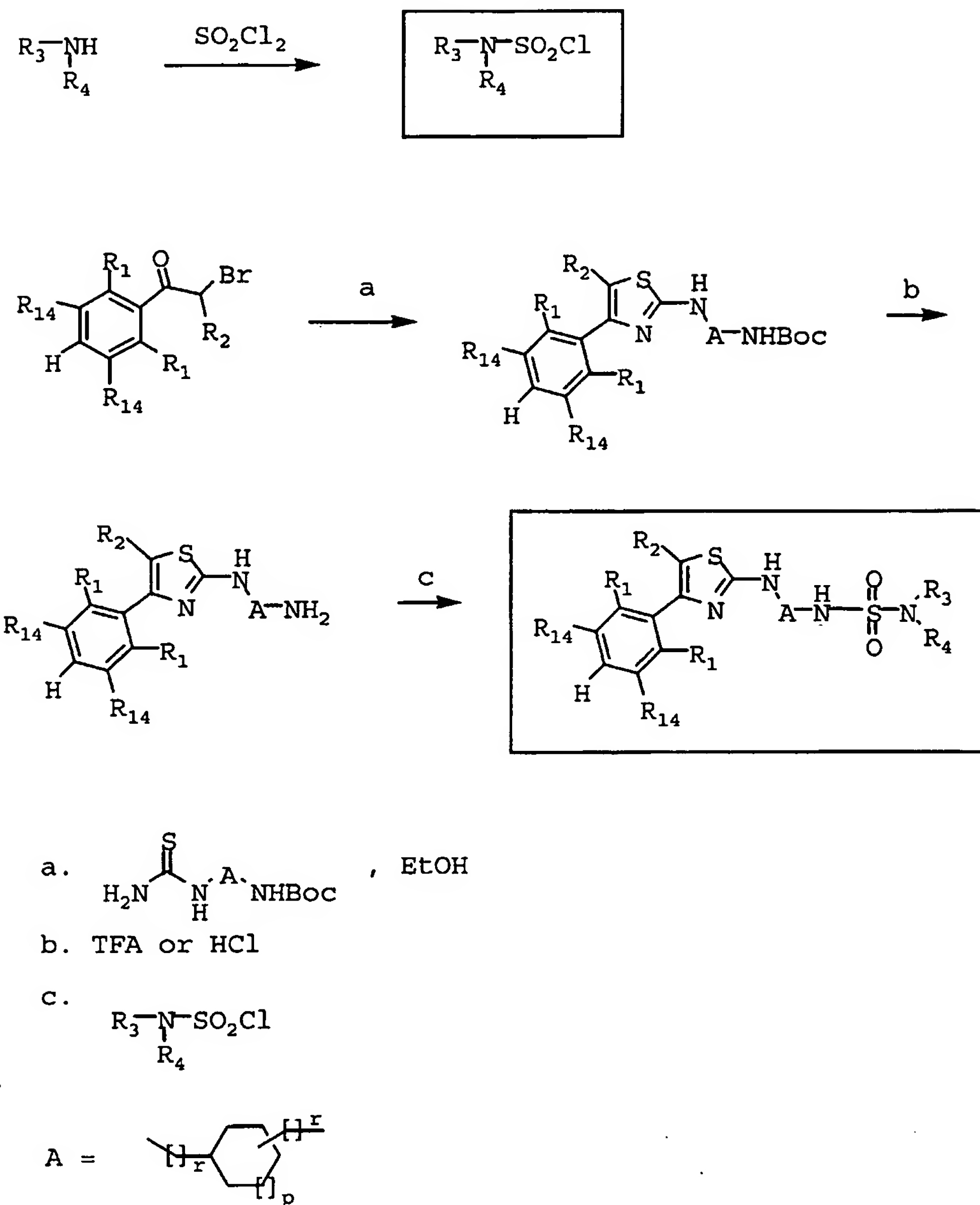
Scheme 8A. Synthesis of Bromoketones



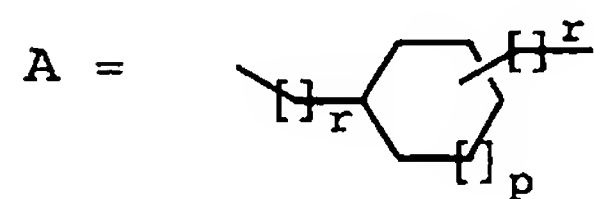
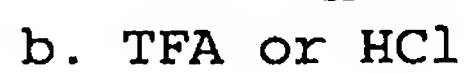
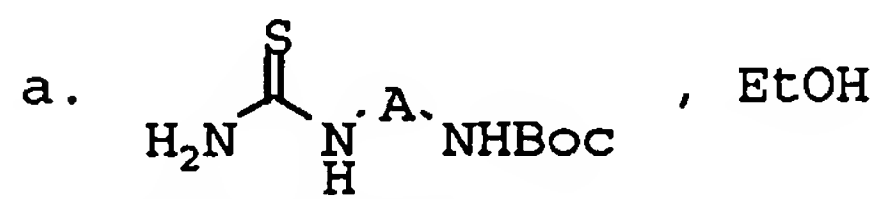
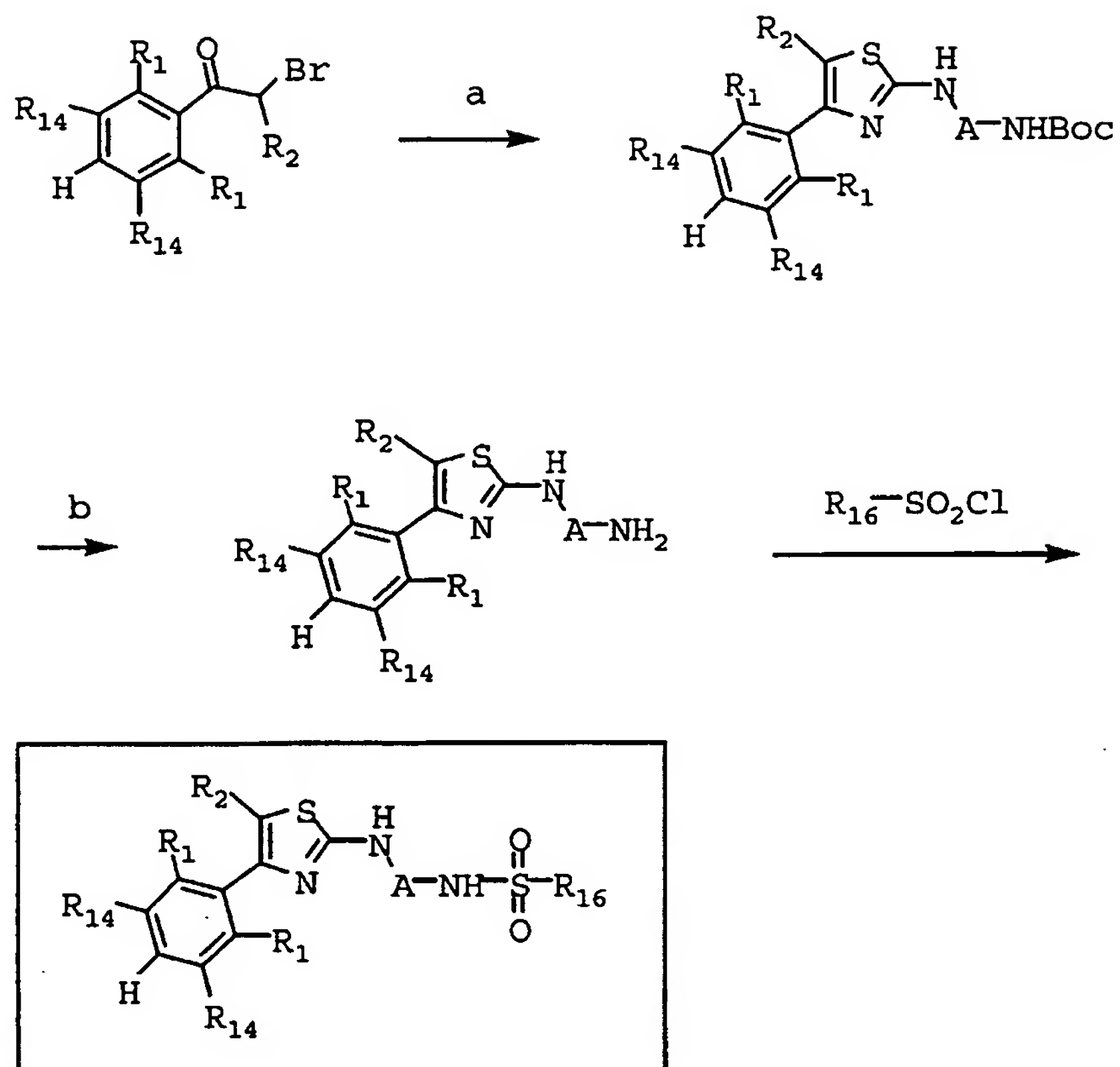
Scheme 8B. Synthesis of Chloroketones



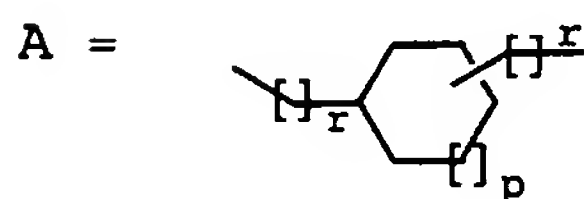
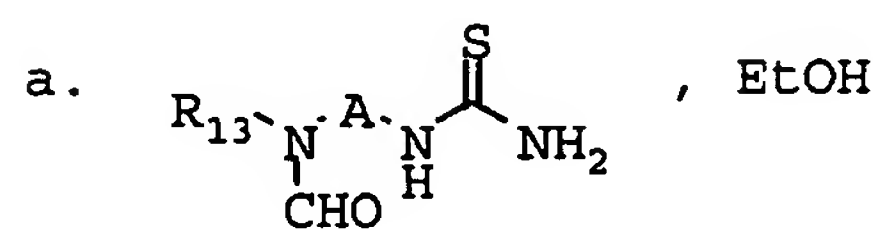
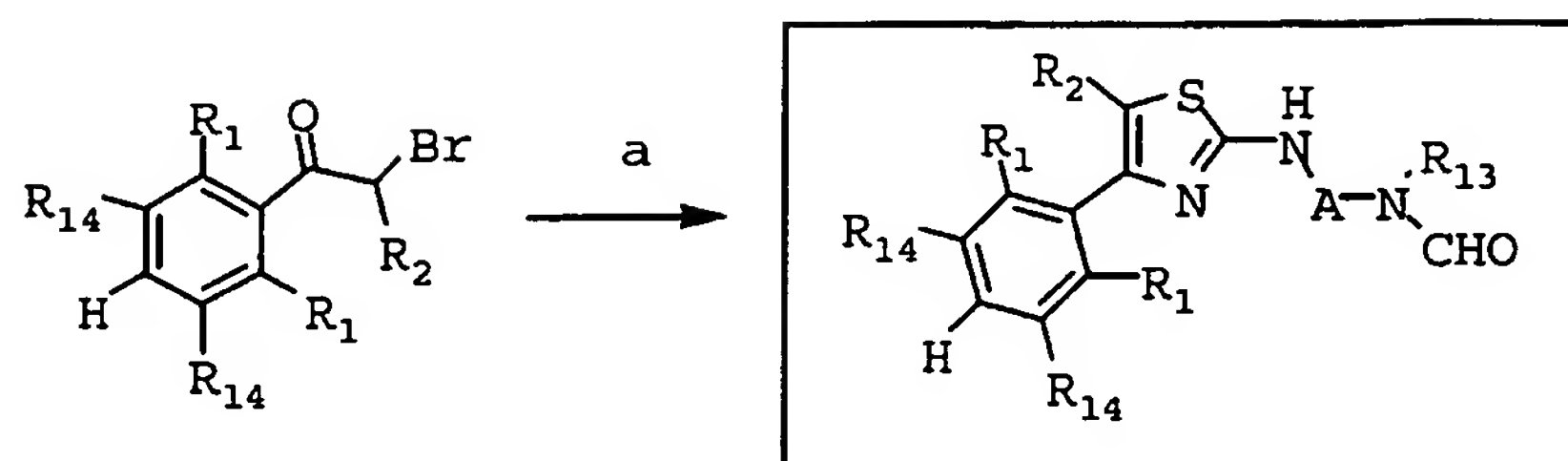
Scheme 9A. Synthesis of the Bicycles



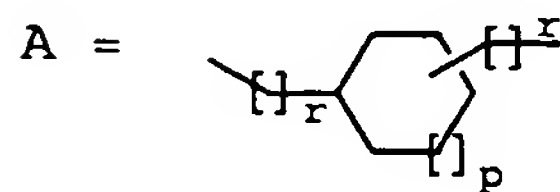
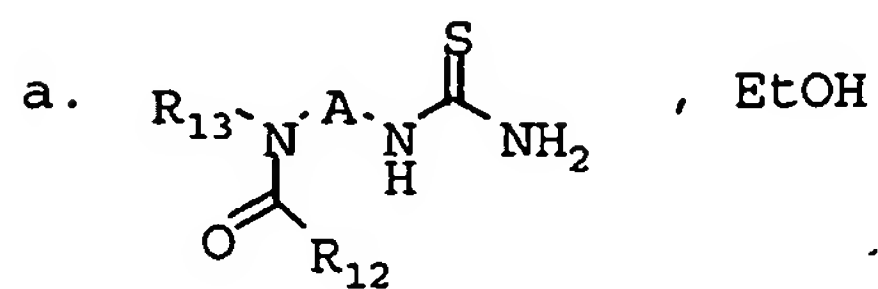
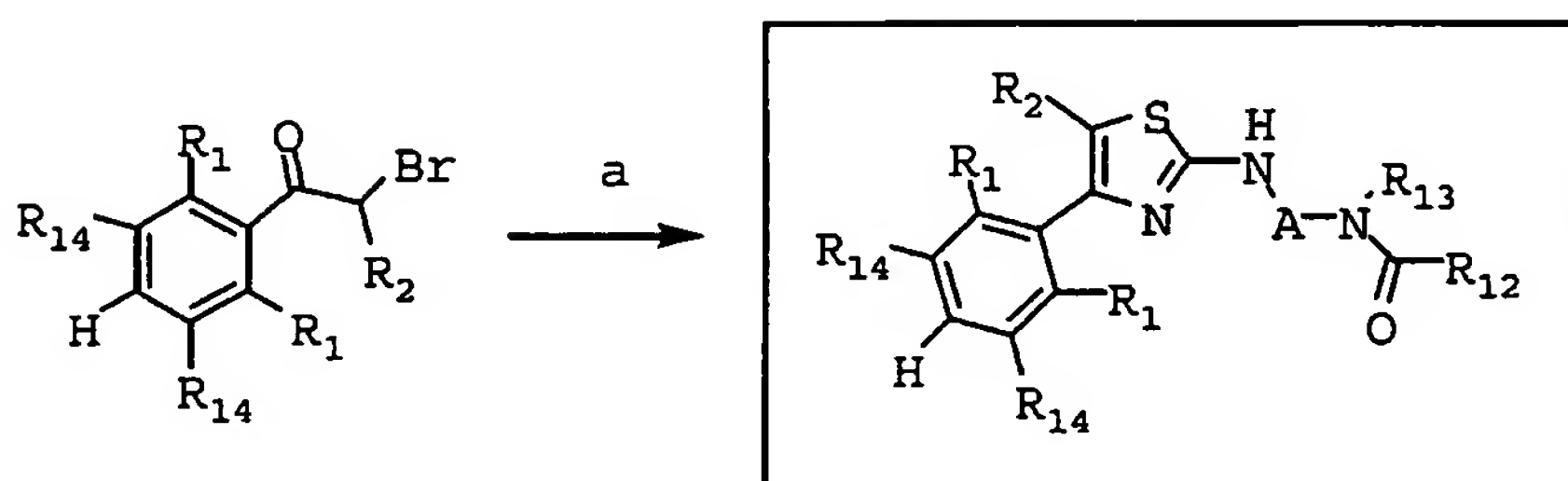
Scheme 9B. Synthesis of the Bicycles



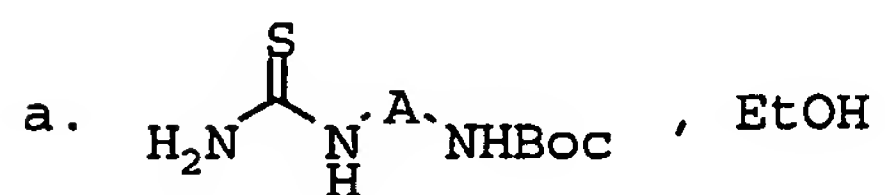
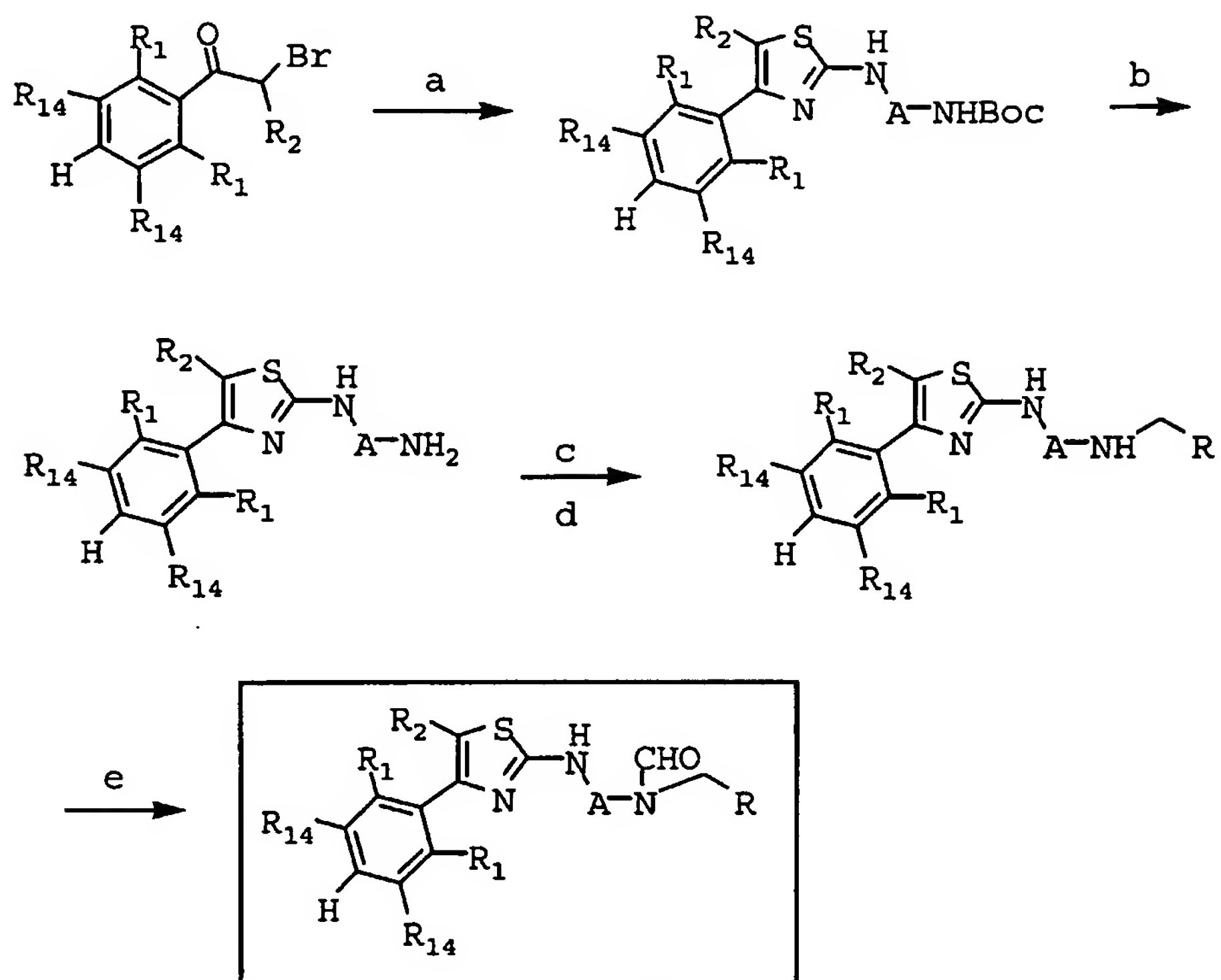
Scheme 9C. Synthesis of the Bicycles



Scheme 9D. Synthesis of the Bicycles



Scheme 9E. Synthesis of the Bicycles

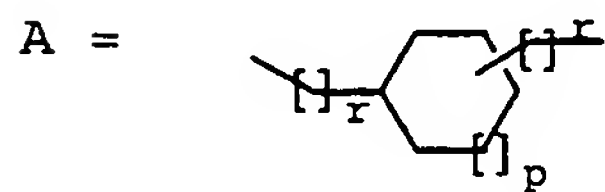


b. TFA or HCl

c. RCOCl

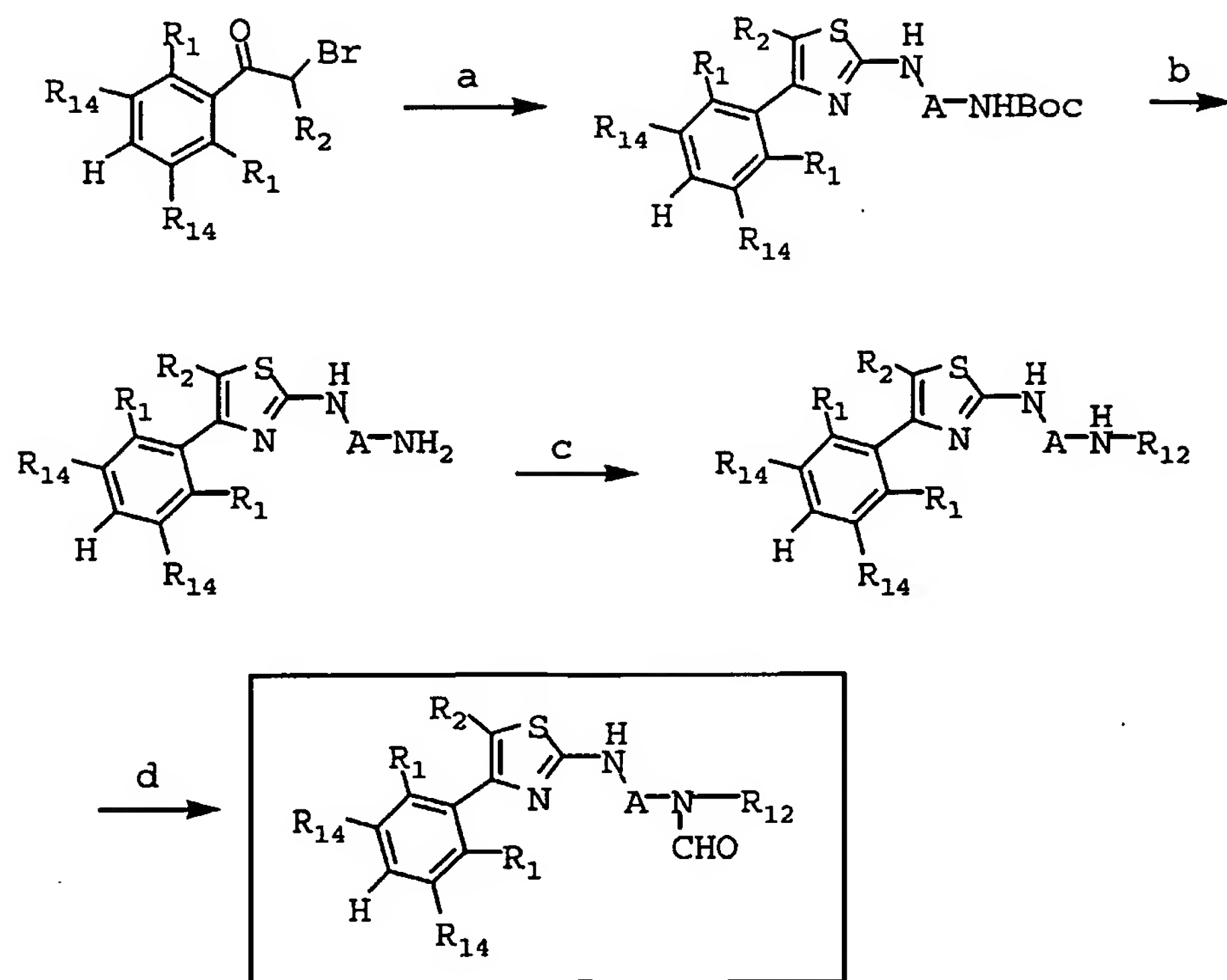
d. reduction

e. formylating agent such as
1H-benzotriazole-1-carboxaldehyde

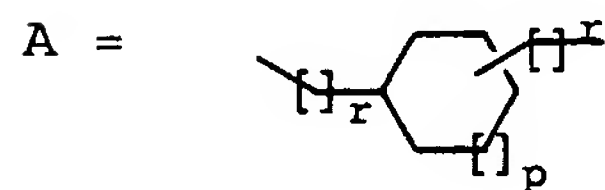


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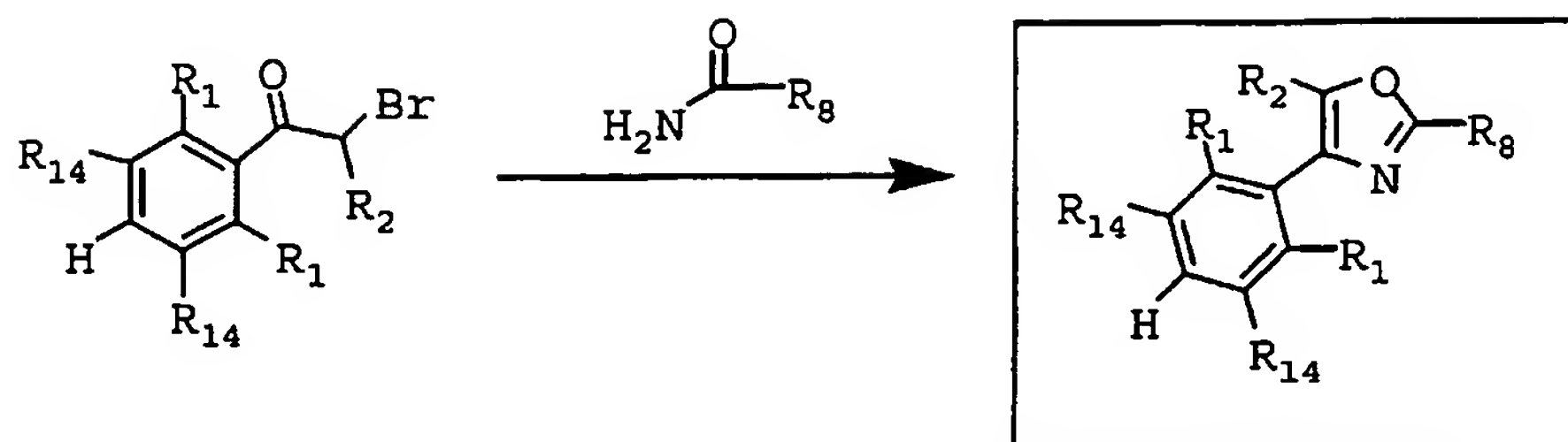
Scheme 9F. Synthesis of the Bicycles



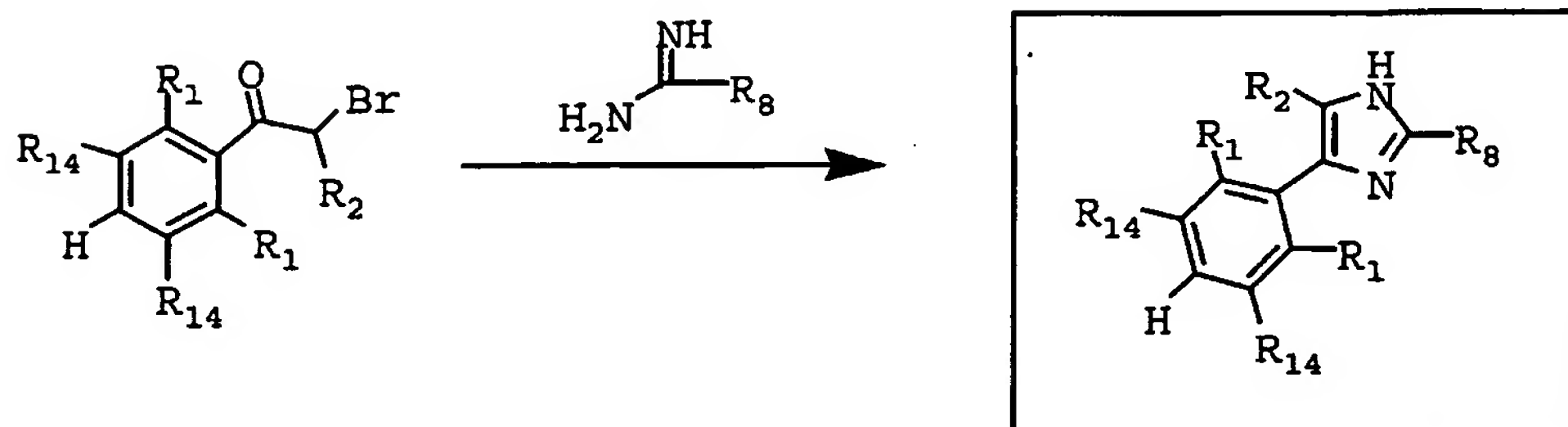
- a. $H_2N-C(=S)-NH-A-NHBoc$, EtOH
- b. TFA or HCl
- c. $R_{12}I$
- d. formylating agent such as
1H-benzotriazole-1-carboxaldehyde

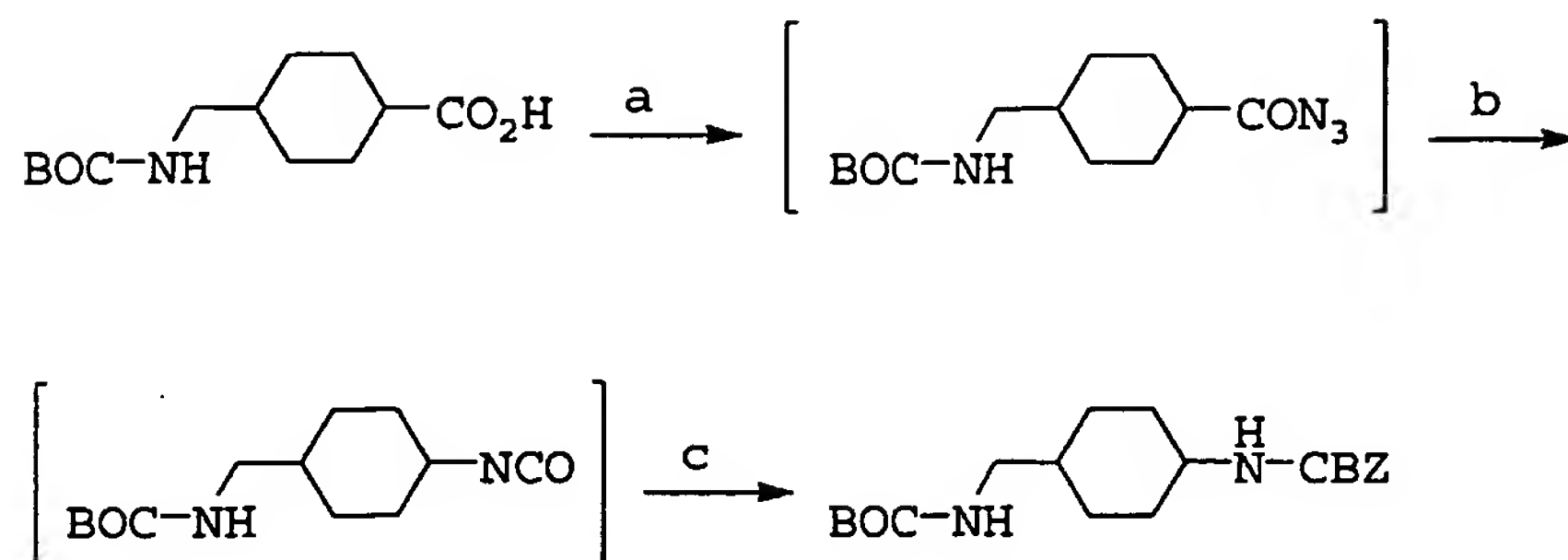


Scheme 10A. Synthesis of Bicycles



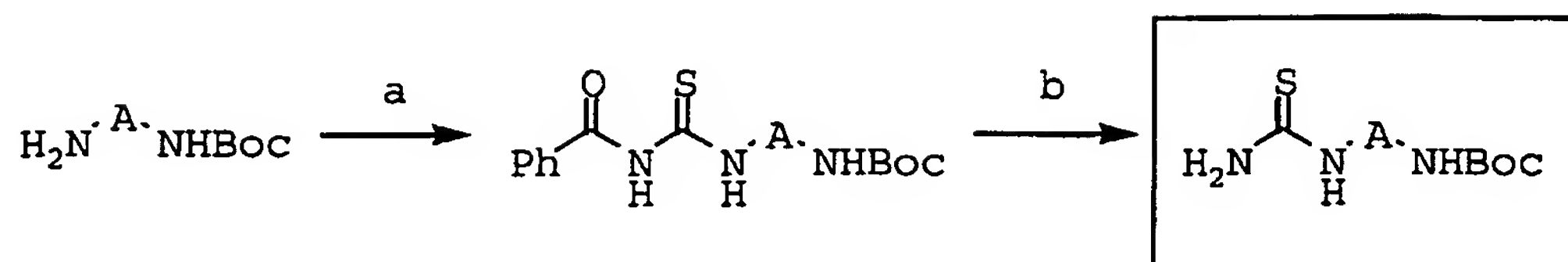
Scheme 10B. Synthesis of Bicycles



Scheme 11: Synthesis of Side Chains

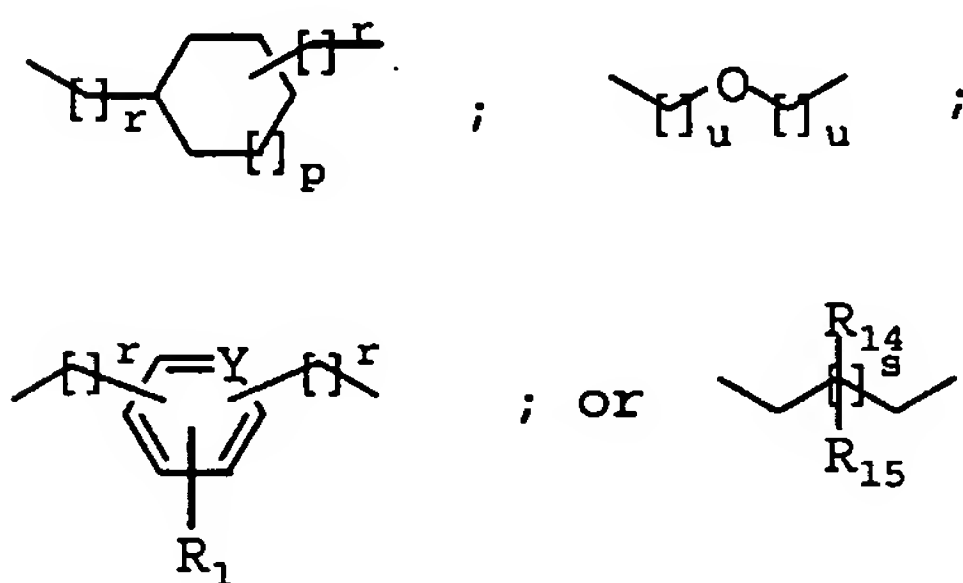
a. Diphenylphosphoryl azide, triethylamine, toluene;
b. heat; c. HOCH2Ph

Scheme 12A. Synthesis of Thioureas

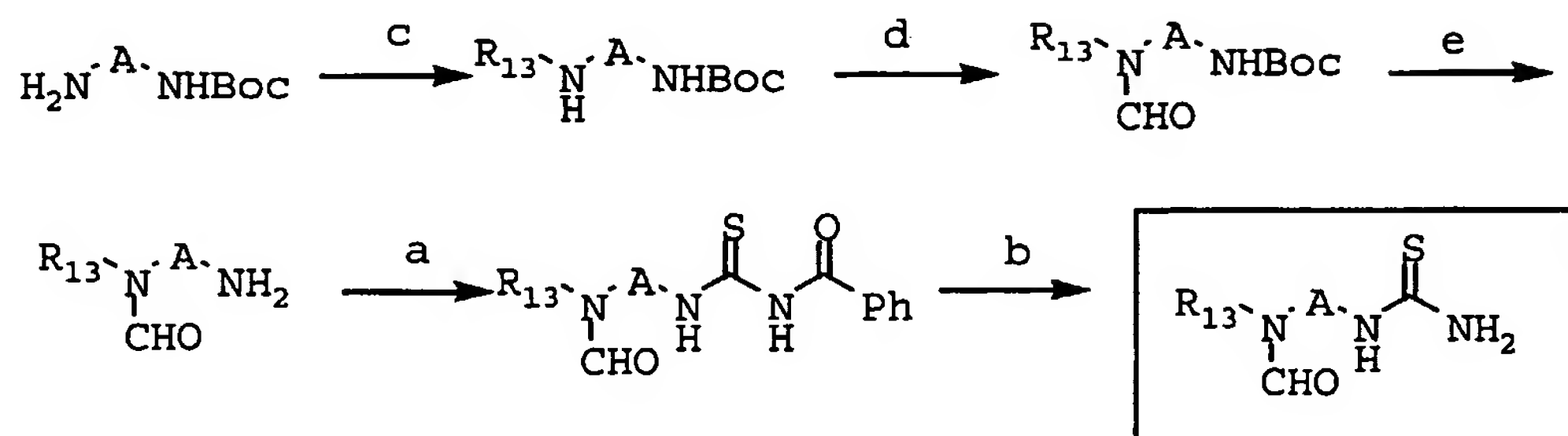


- a. benzoylisothiocyanate
b. K_2CO_3 , MeOH

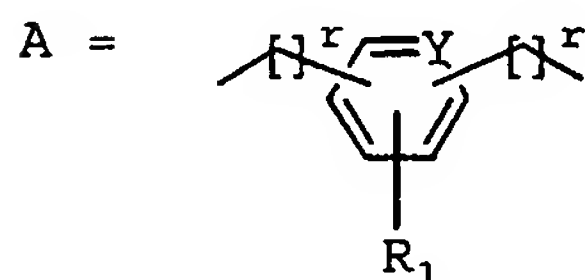
A =



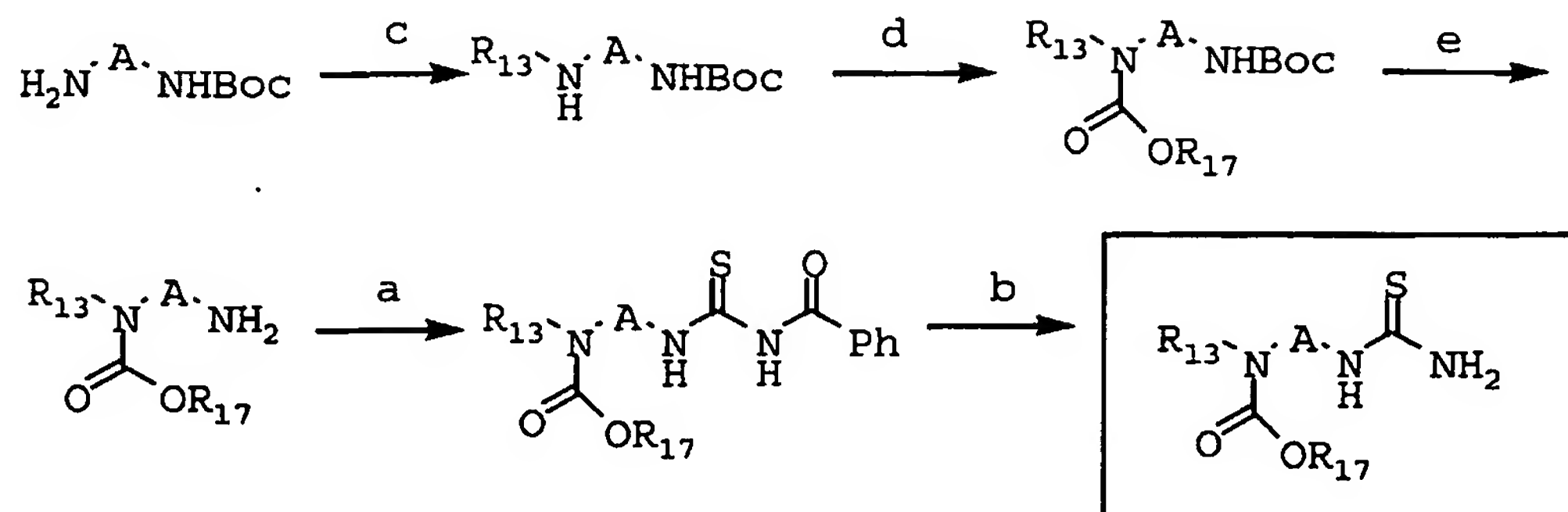
Scheme 12B. Synthesis of Thioureas



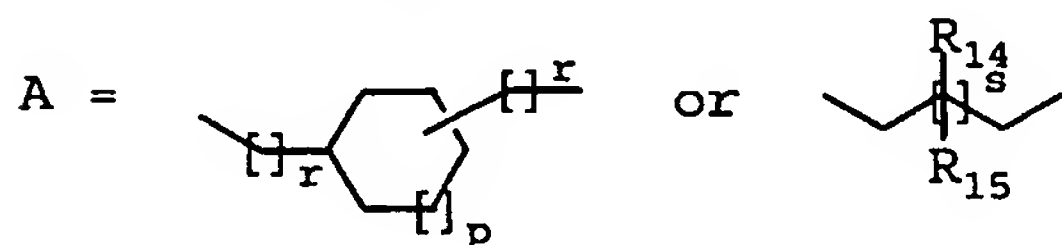
- a. Benzoylisothiocyanate
b. K_2CO_3 , MeOH
c. alkyl halide or acyl halide followed by borane reduction.
d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde
e. HCl or TFA



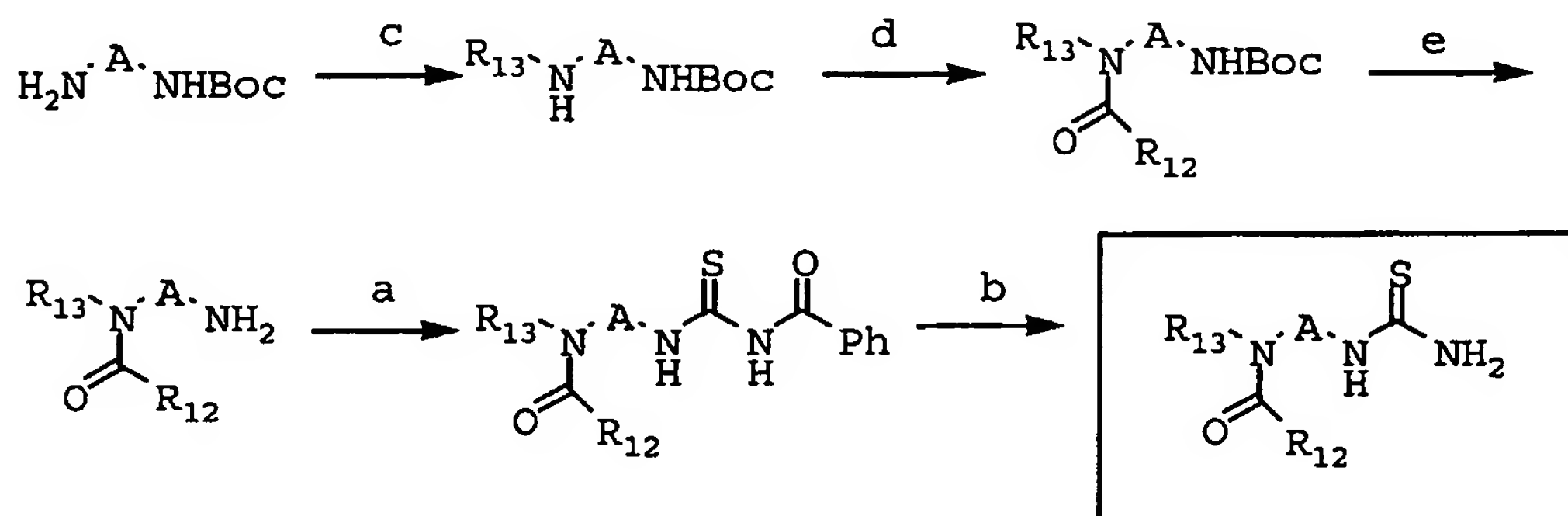
Scheme 12C. Synthesis of Thioureas²⁴³



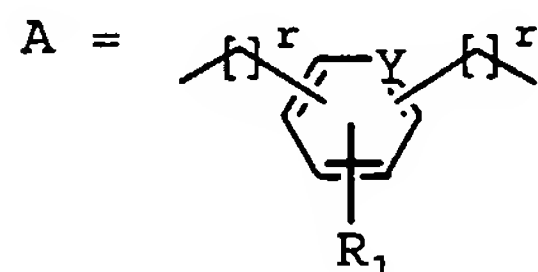
- a. Benzoylisothiocyanate
 b. K_2CO_3 , MeOH
 c. alkyl halide or acyl halide followed by borane reduction
 d. $\text{R}_{17}\text{OCOCl}$
 e. HCl or TFA



Scheme 12D. Synthesis of Thioureas

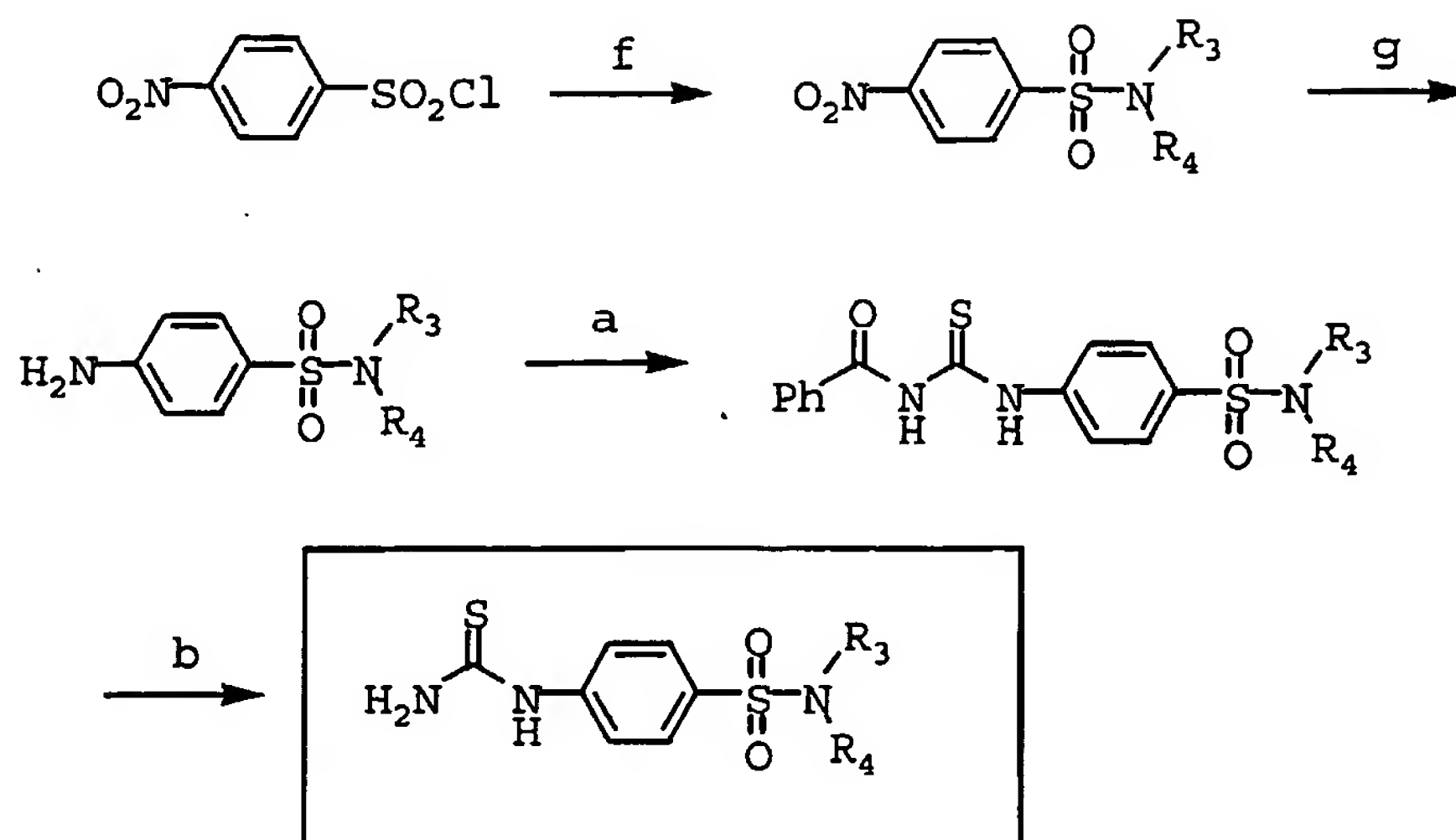


- a. Benzoylisothiocyanate
 b. K_2CO_3 , MeOH
 c. alkyl halide or acyl halide followed by borane reduction
 d. R_{12}COCl
 e. HCl or TFA



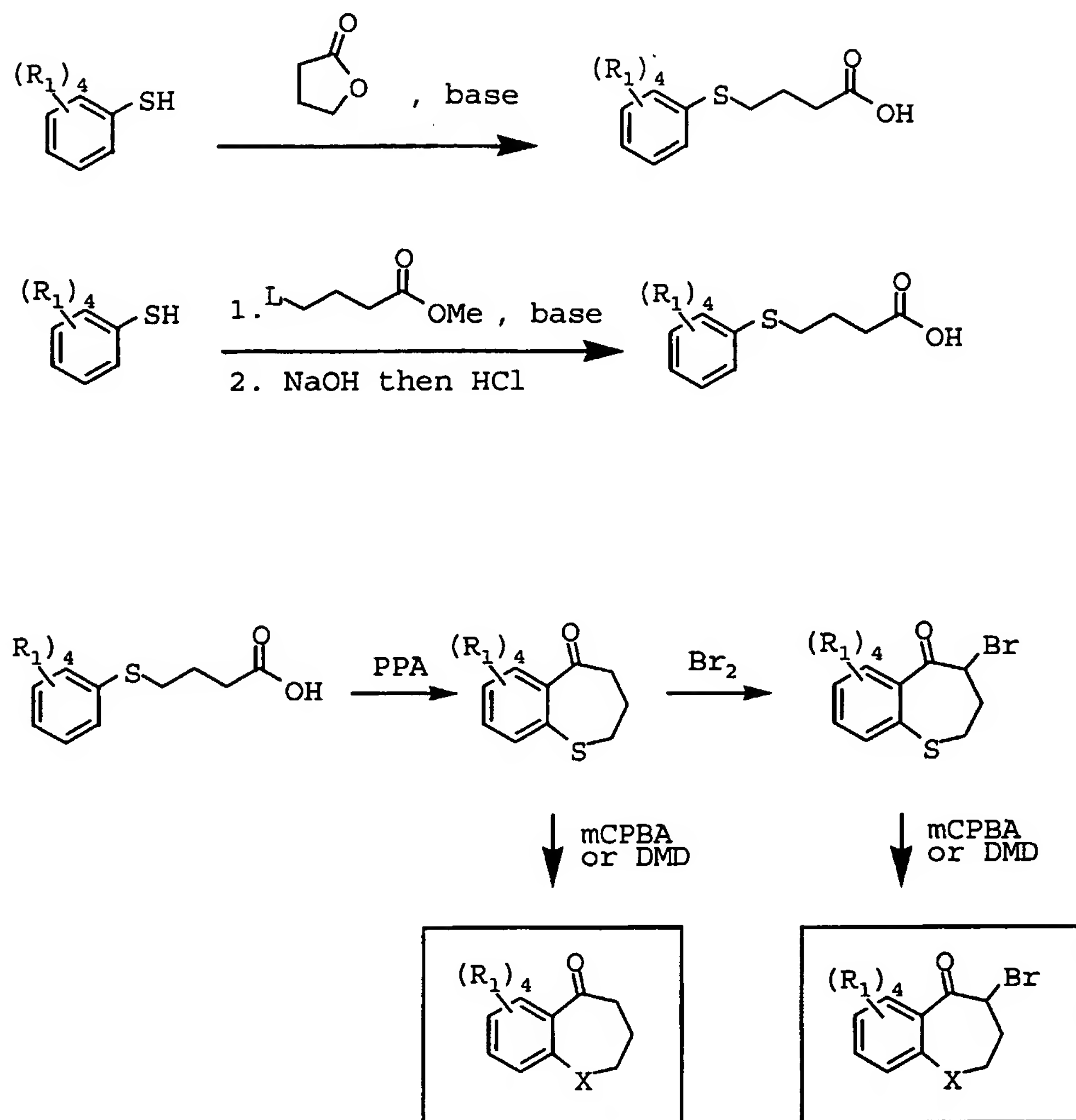
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Scheme 12E. Synthesis of Thioureas



- a. benzoylisothiocyanate
- b. K_2CO_3 , MeOH
- f. HNR_3R_4
- g. reduction

Scheme 13. Synthesis of Bromoketones



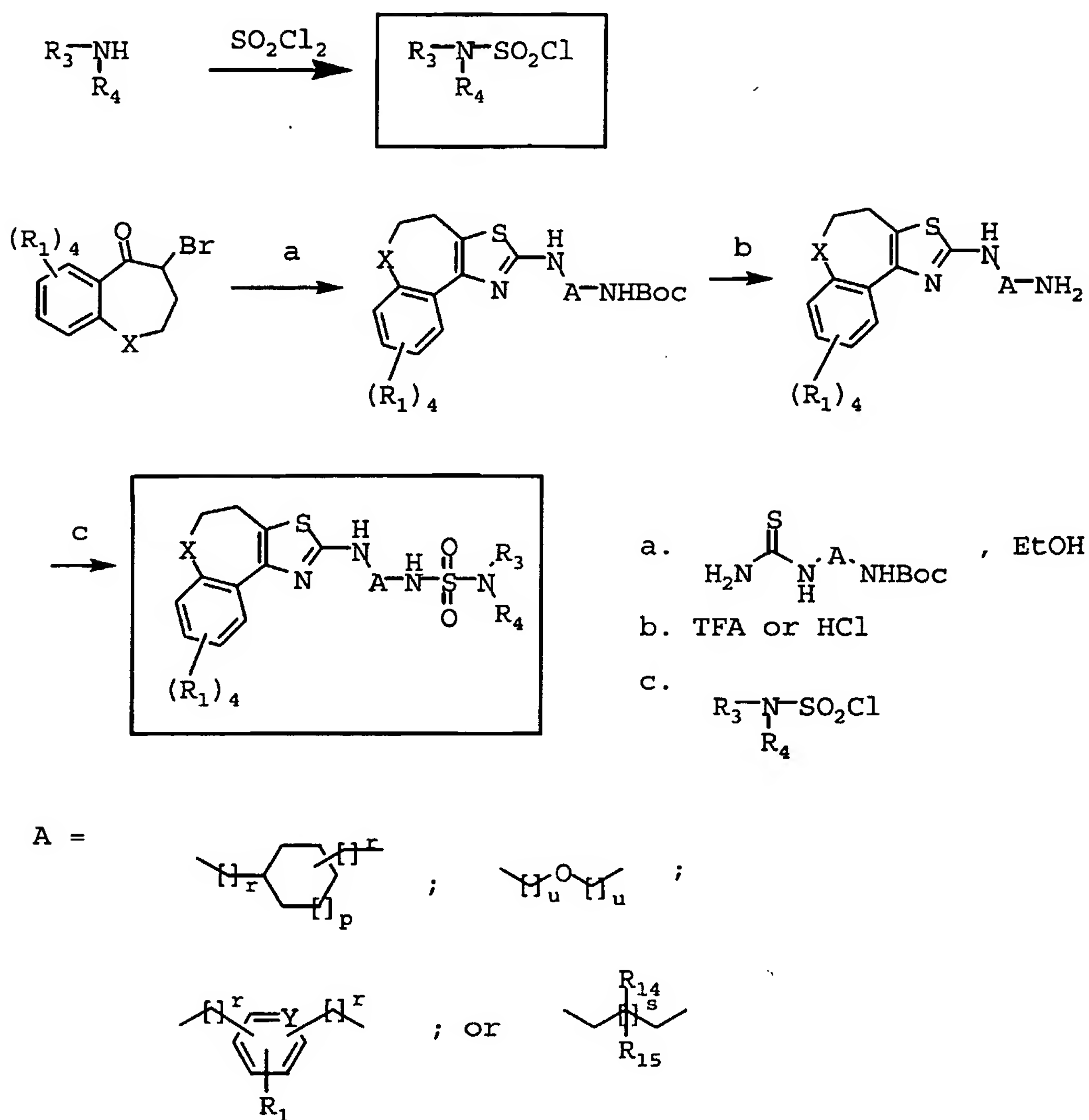
L = leaving group such as Br

X = S, SO, SO₂

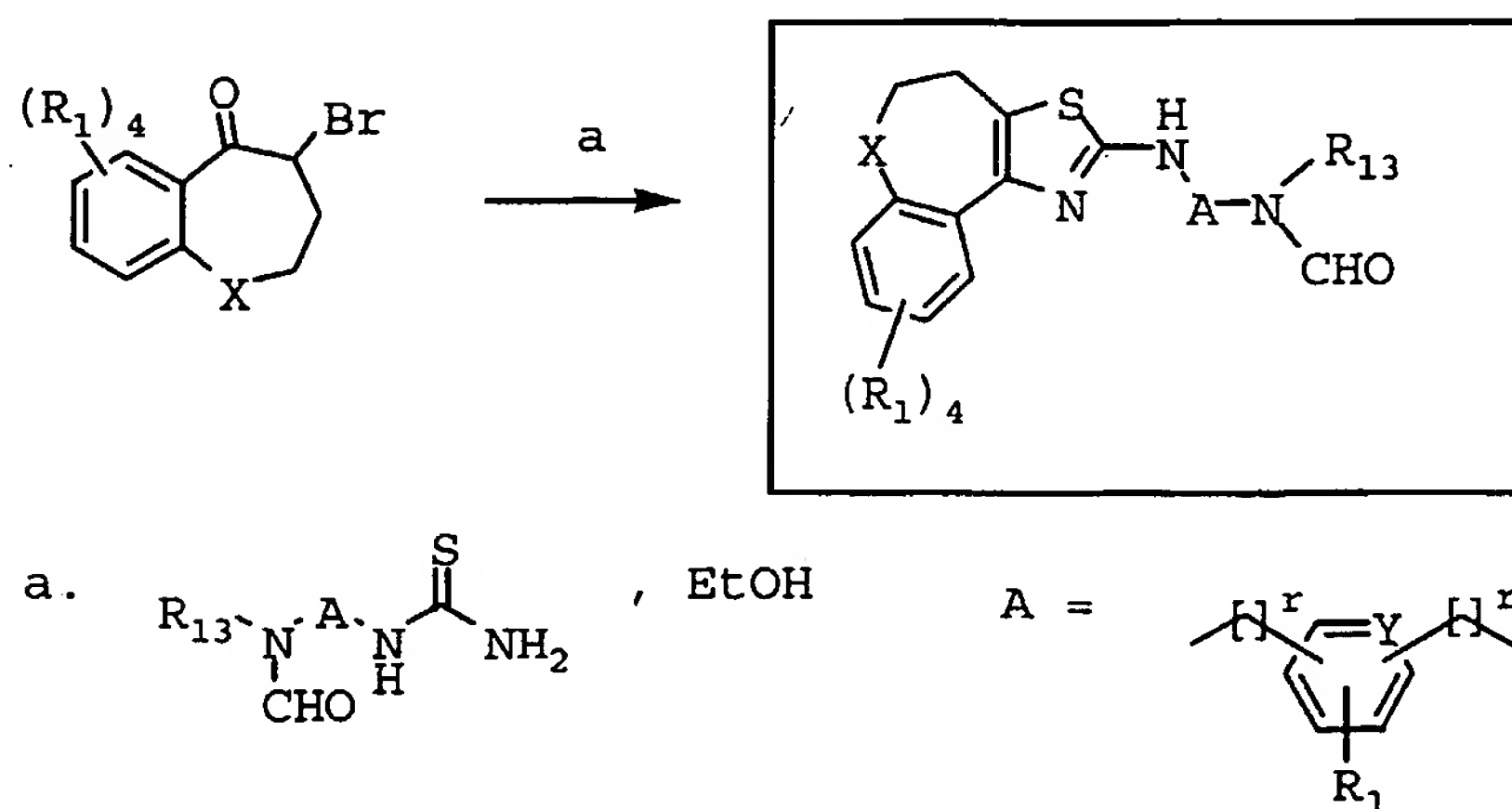
DMD = dimethyldioxirane

mCPBA = m-chloroperbenzoic acid

Scheme 14A. Synthesis of the Tricycles

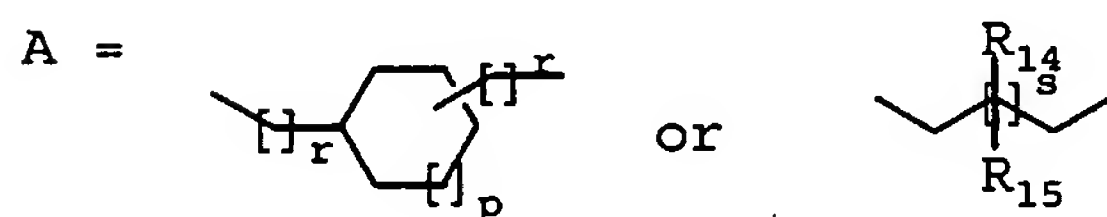
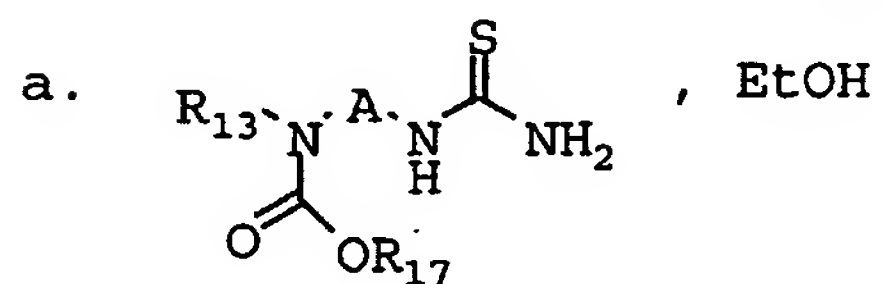
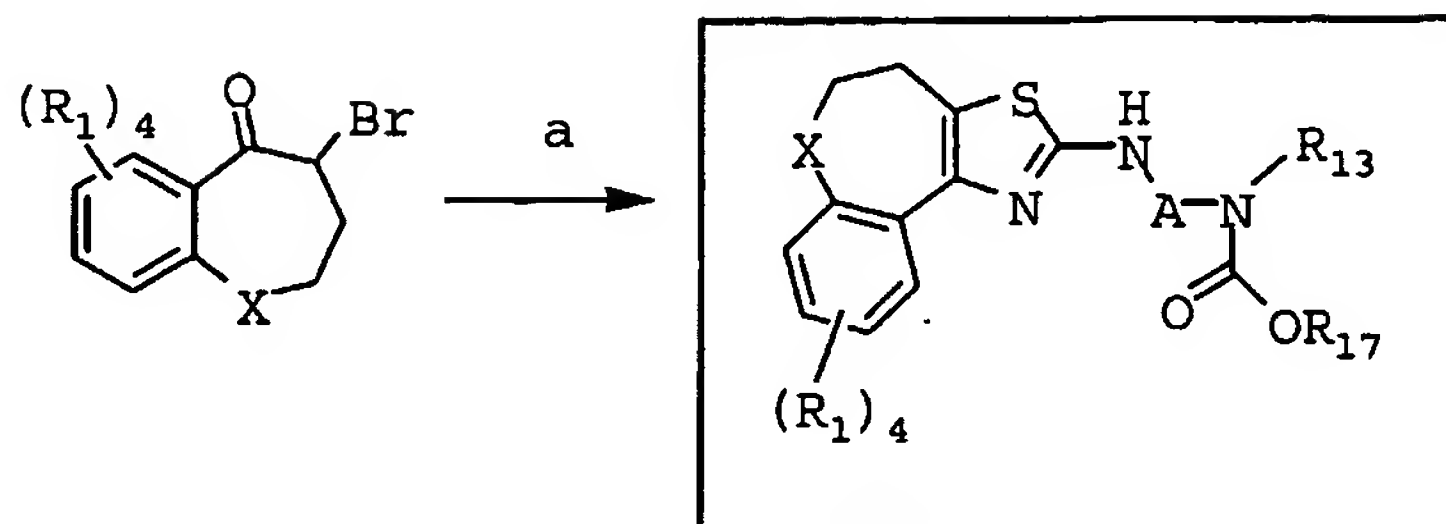


Scheme 14B. Synthesis of the Tricycles

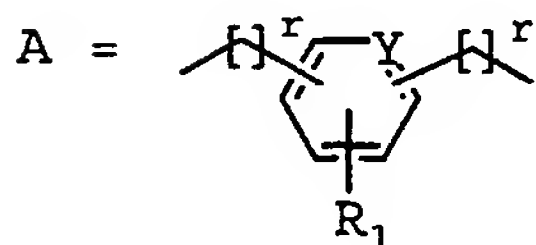
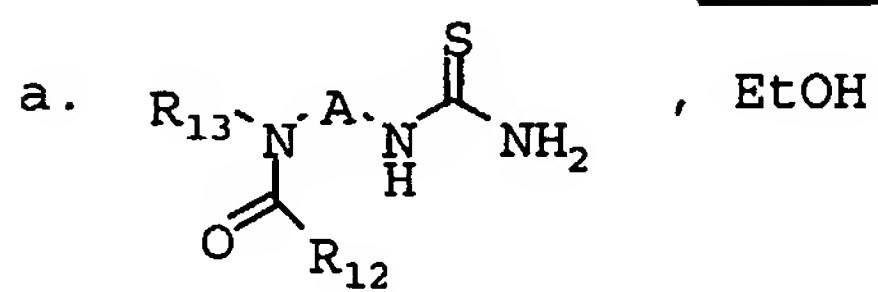
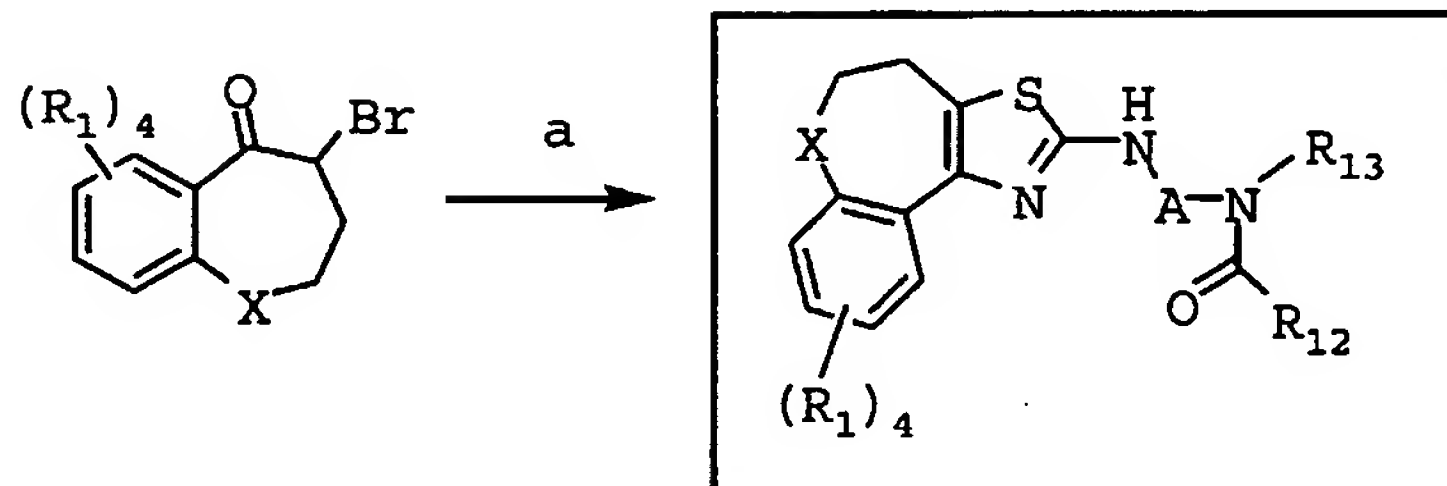


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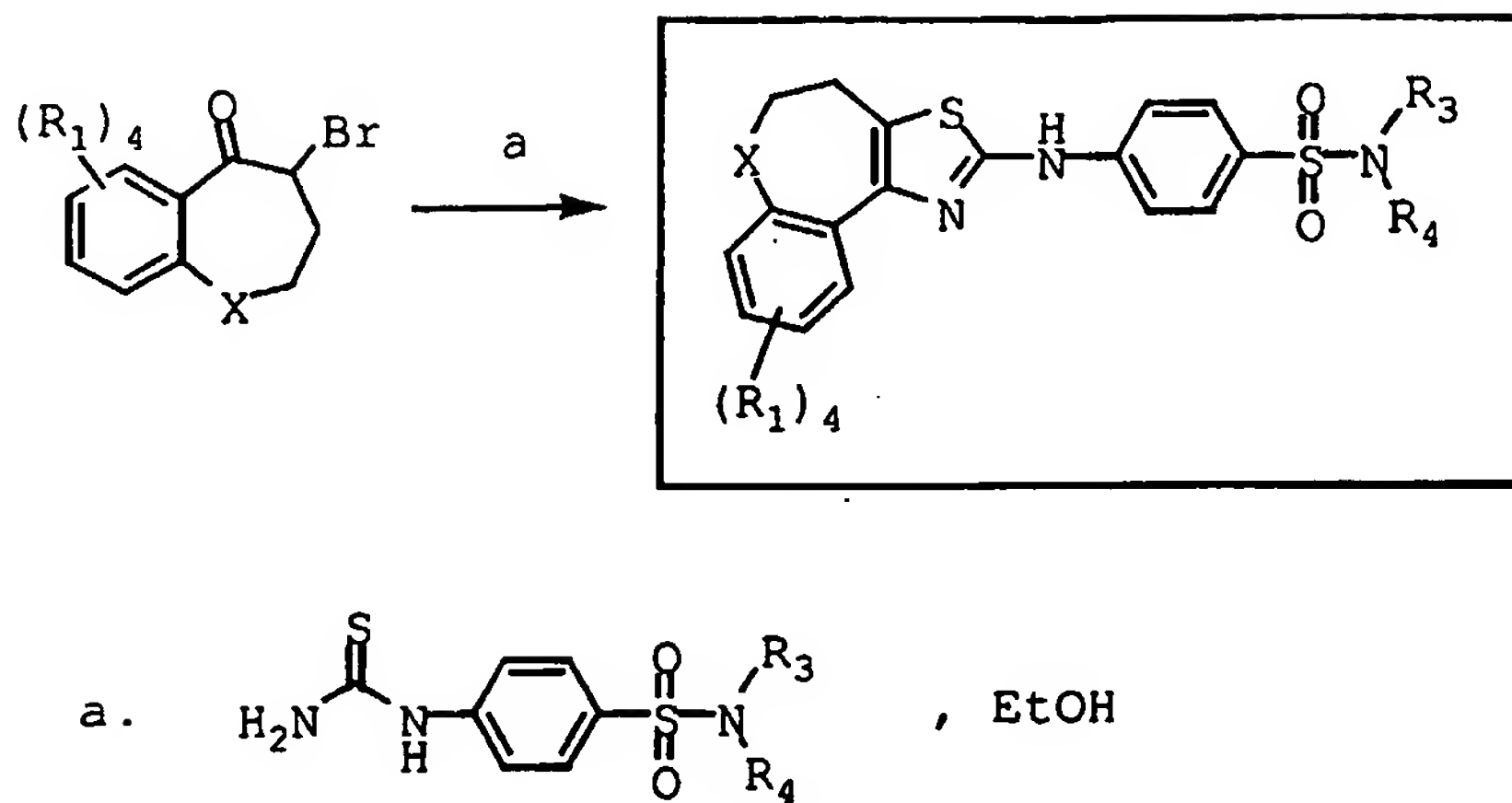
Scheme 14C. Synthesis of the Tricycles



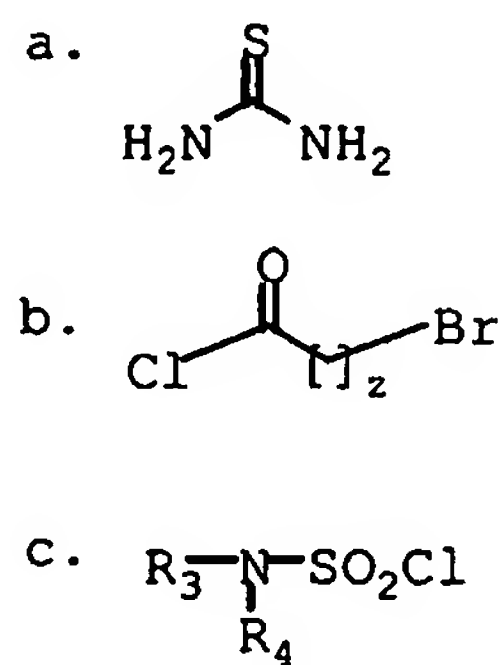
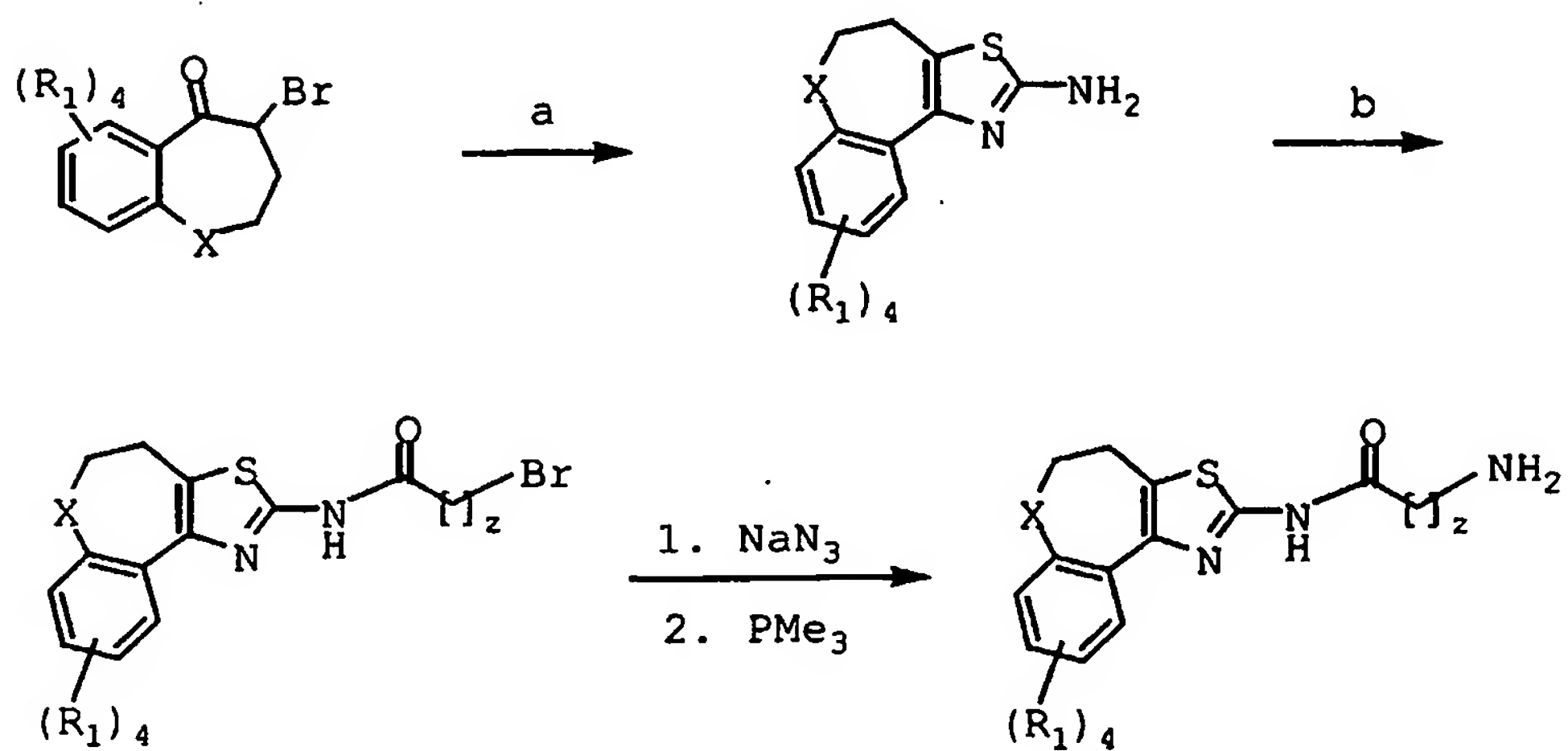
Scheme 14D. Synthesis of the Tricycles

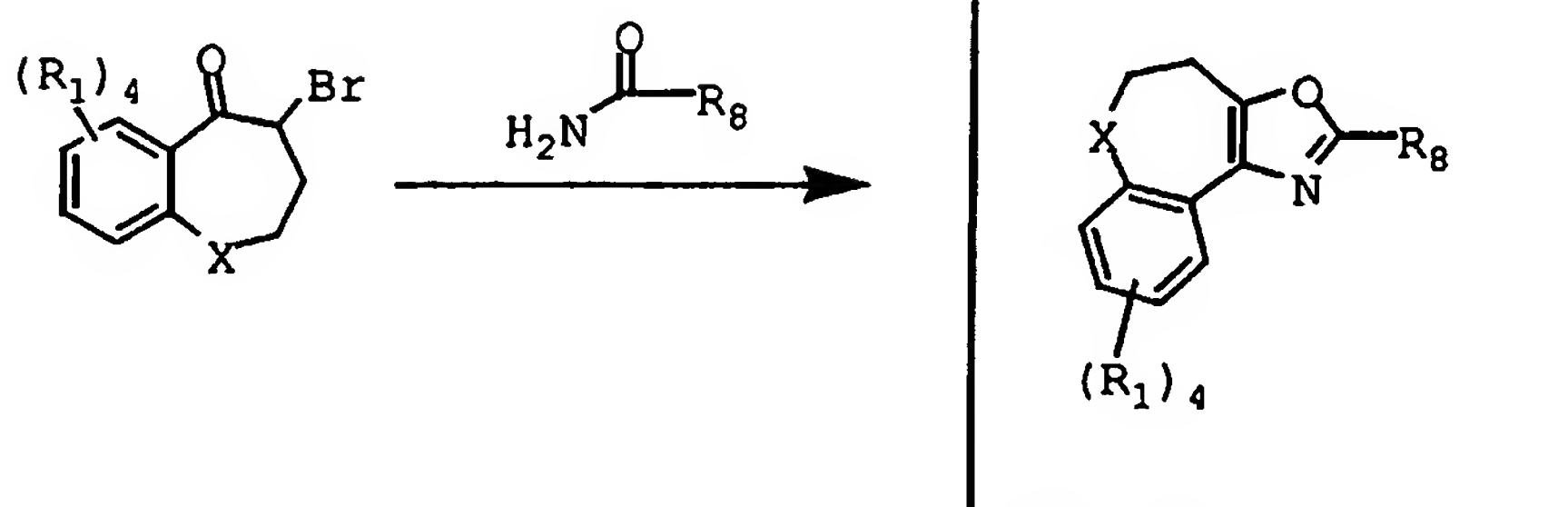
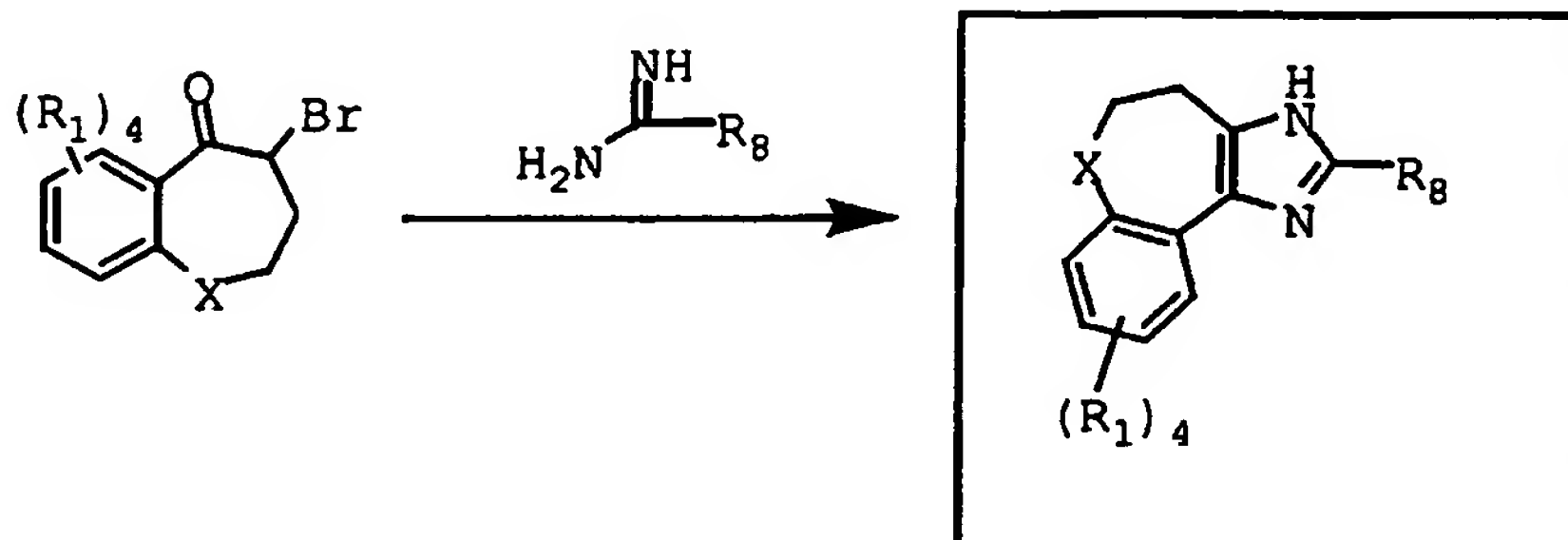


Scheme 14E. Synthesis of the Tricycles

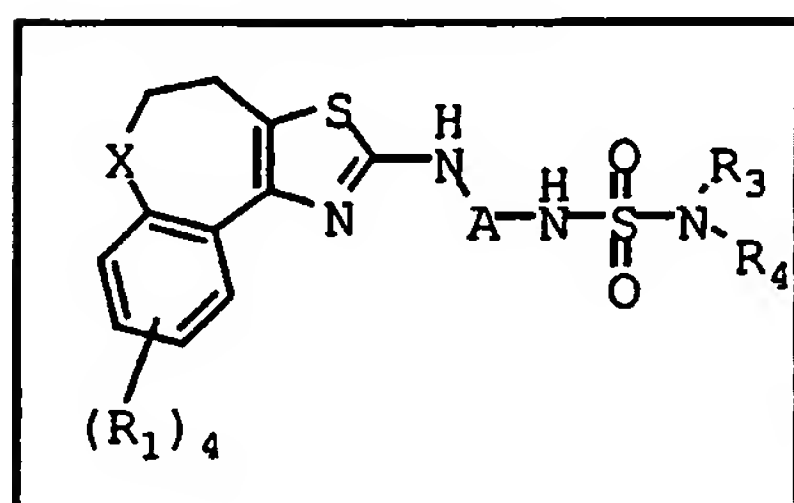
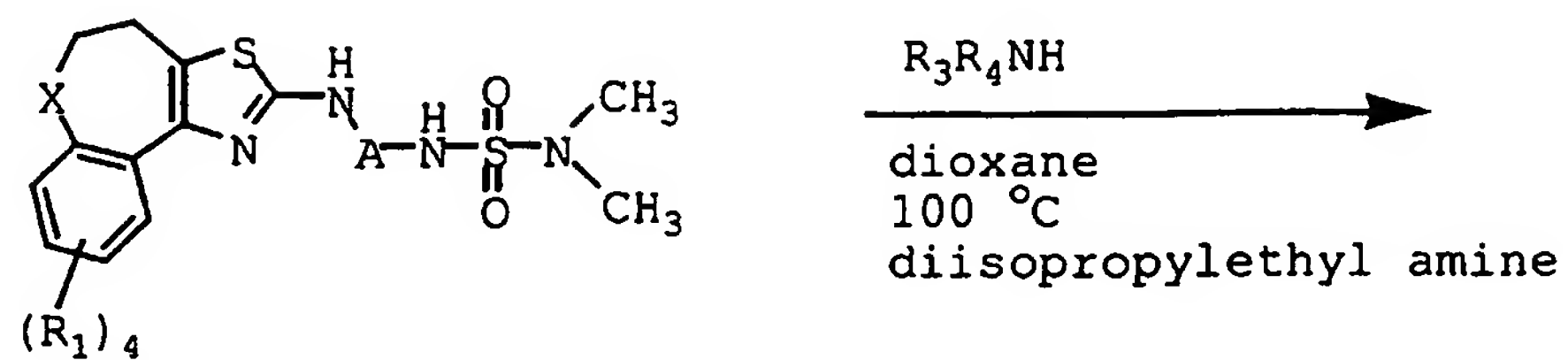


Scheme 14F. Synthesis of the Tricycles

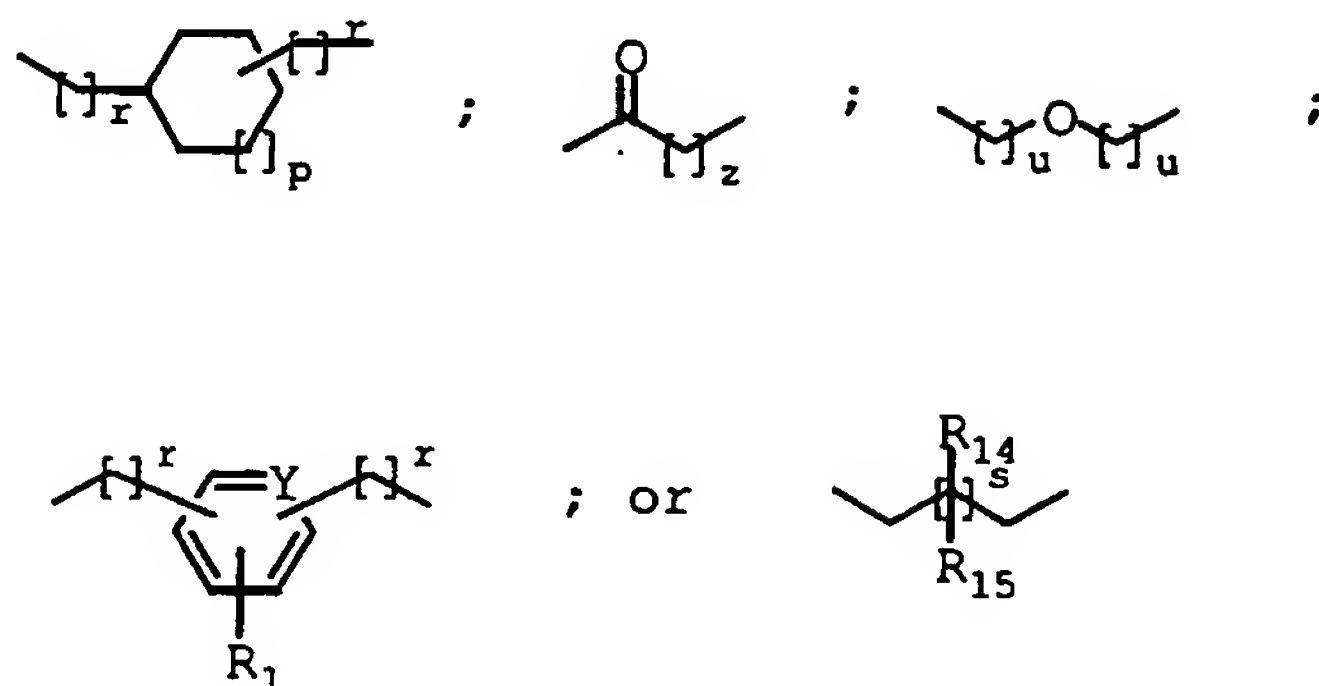


Scheme 15A. Synthesis of Tricycles**Scheme 15B. Synthesis of Tricycles**

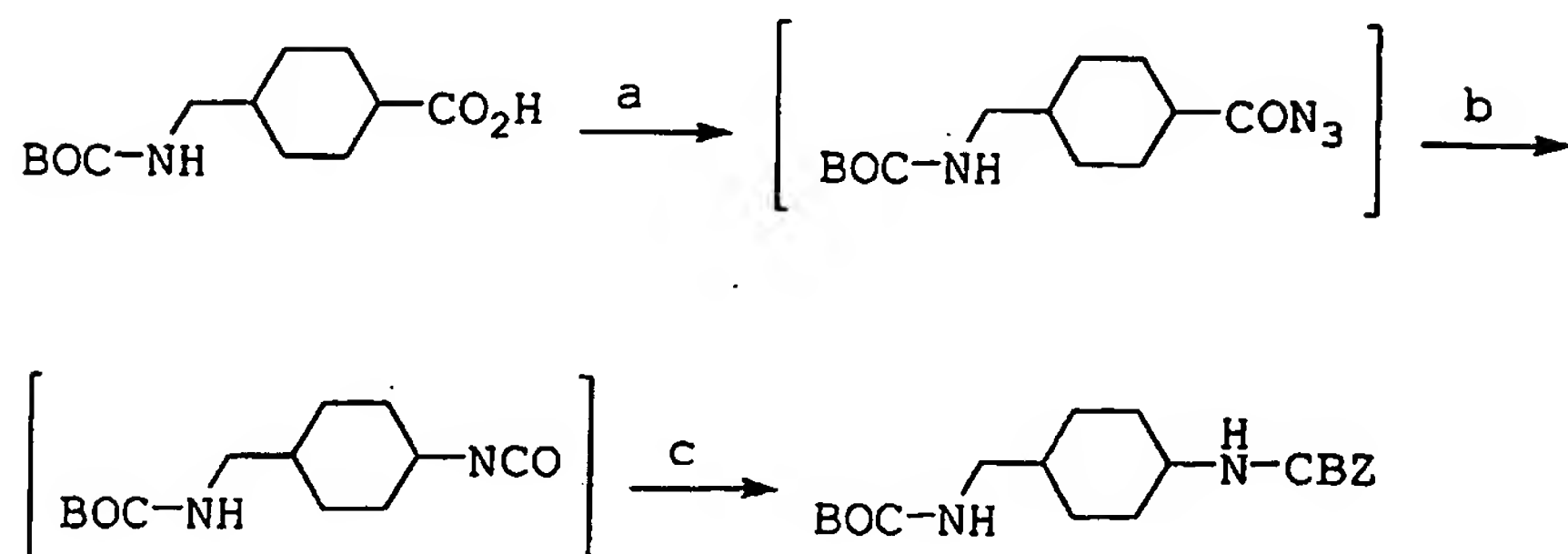
Scheme 16. Transamination of Sulfonylureas



A =



Scheme 17: Synthesis of Side Chains



a. Diphenylphosphoryl azide, triethylamine, toluene;
 b. heat; c. HOCH₂Ph

Functional Assay Results

The functional in vitro activity of several compounds were characterized using a radioimmunoassay of cAMP, the results of which are summarized in Table 4.

Table 4. Functional Antagonism Data

Example #	K _i (h NPY-5), nM	pK _b
1	2.1	7.9
3	4.5	8.5
4	19.5	8.6
11	6.4	8.5
15	3.2	8.6
20	0.3	8.3
34	33.5	7.2
43	4.4	7.8
44	2.3	8.8
50	15.3	8.1
79	20.1	7.9
80	32.9	7.4

References

- Balasubramaniam, A., Sheriff, S., Johnson, M. E., Prabhakaran, M., Huang, Y., Fischer, J. E., and Chance, W. T. (1994). [D-Trp³²]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 3
- Bradford, M. M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal. Biochem. 72: 248-254.
- Chabaka, L. M., et al., "Facile Synthesis of 2-Furyl-, 2-Pyrrolyl-, 2-Imidazolyl- and Pyrrolo- Azoles from 2-Substituted Methylazoles." Pol. J. Chem. (1994) 68(7): 1317-1325.
- Clark, J. T., Kalra, P. S., Crowley, W. R., and Kalra, S. P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 115: 427-429.
- Crangk, G. and Foulis, M.J., " Oxazoles from ureas" J. Med. Chem. (1971) 14: 1075.
- Criscione, L., Rigollier, P., Batzl-Hartmann, C., Rueger, H., Stricker-Krongrad, A., Wyss, P., Brunner, L., Whitebread, S., Yamaguchi, Y., Gerald, C., Heurich, R. O., Walker, M. W., Chiesi, M., Schilling, W., Hofbauer, K. G., Levens, N. (1998) Food intake in free-feeding and energy-deprived lean rats is mediated by the neuropeptide Y5 receptor. J. Clin. Invest. 102(12): 2136-45.

Critcher, D.J. and Pattenden, G., " Synthetic Studies Towards Pateamine, a Novel Thiazole-Based 19- Membered Bis-lactone from Mycale sp." Tetrahedron. Lett. (1996) 37(50): 9107-9110.

Cullen, B. (1987). Use of eukaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704.

De Kimpe, N., et al., "Synthesis of 2-Imino-4-thiazolines, 2-Imino-4-alkoxythiazolidines, Thiazoles, and 4-Imidazolin-2-ones from alpha-Halomethyl Ketimines.", *J. Heterocycl. Chem.* (1996) 33(4): 1179-1183.

Demchenko, A. M., et al., " Preparation and Application of alpha -Bromomono- and -bisdifluoromethoxyacetophenones in the Course of Synthesis of Polymethyleneimidazoles Containing a Bridge Nitrogen Atom", Khim. Geterotsikl. Soedin. (1997) 10: 1371-1376.

Di Fabio, R. and Pentassuglia, G., "Novel Synthesis of Ethyl 3-(Bromoacetyl)-4,6-dichloro-1H-indole-2-carboxylate as Useful Intermediate in the Preparation of Potential Glycine Site Antagonists", Synth. Commun. (1998) 28(1): 51-60.

Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308.

Dumont, Y., Martel, J.-C., Fournier, A., St-Pierre, S., and Quirion, R. (1992). Neuropeptide Y and neuropeptide Y

receptor subtypes in brain and peripheral tissues.
Progress in Neurobiology 38: 125-167.

5 Eva, C., Oberto, A., Sprengel, R. and Genazzani, E.
(1992). The murine NPY-1 receptor gene: structure and
delineation of tissue specific expression. FEBS Lett.
314: 285-288.

10 Eva, C., Keinänen, K., Monyer, H., Seeburg, P., and
Sprengel, R. (1990). Molecular cloning of a novel G
protein-coupled receptor that may belong to the
neuropeptide receptor family. FEBS Lett. 271: 80-84.

15 Friedman, B. S., et al., "Thiazoles from thioamides", J.
Am. Chem. Soc. (1937) 59: 2262.

Hammar, W.J. and Rustad, M.A., "Oxazoles from alpha-
bromoketones" J. Heterocycl. Chem. (1981) 18: 885.

20 Herzog, H., Hort, Y. J., Ball, H. J., Hayes, G., Shine,
J., and Selbie, L. (1992). Cloned human neuropeptide Y
receptor couples to two different second messenger
systems. Proc. Natl. Acad. Sci. USA 89: 5794-5798.

25 Kalra, S. P., Dube, M. G., Fournier, A., and Kalra, P. S.
(1991). Structure-function analysis of stimulation of
food intake by neuropeptide Y: Effects of receptor
agonists. Physiology & Behavior 50: 5-9.

30 Kearney, P. C., et al., "Solid-Phase Synthesis of 2-
Aminothiazoles", J. Org. Chem. (1998) 63(1): 196-200.

Larhammar, D., Blomqvist, A. G., Yee, F., Jazin, E., Yoo,
H., and Wahlestedt, C. (1992). Cloning and functional

255

expression of a human neuropeptide Y/peptide YY
receptor of the Y1 type. J. Biol. Chem. 267: 10935-10938.

Levine, A. S., and Morley, J. E. (1984). Neuropeptide Y:
5 A potent inducer of consummatory behavior in rats.
Peptides 5: 1025-1029.

Little, T. L. and Webber, S. E., "A Simple and Practical
Synthesis of 2-Aminoimidazoles" J. Org. Chem. (1994)
10 59(24): 7299-7305.

Marchetti, E., et al., "Oxazoles from ureas" J. Med. Chem.
(1968) 11: 1092.

15 Michel, M.C. (1991). Receptors for neuropeptide Y:
multiple subtypes and multiple second messengers. Trends
Pharmacol. 12: 389-394.

Nagao, Y., et al., "Novel Nonprostanoid Prostacyclin
20 (PGI₂) Mimetics with Heterocyclic Moiety", Heterocycles
(1996) 42(2): 517-523.

Novikova, A. P., et al., "Synthesis and Properties of
1,3,4-Thiadiazine Derivatives. Part 1. Condensation of
25 Substituted Phenacyl Bromides and Bromoacetylpyridines
with Thiosemicarbazide", Khim. Geterotsikl. Soedin. (1991)
(6): 843-846.

Pathak, V.N., et al., "Synthesis of Some New Fluorine
30 Containing Oxazoles, Oxadiazoles, Thiadiazoles and
Triazines"; J. Indian Chem. Soc. (1993) 70(6): 539-542.

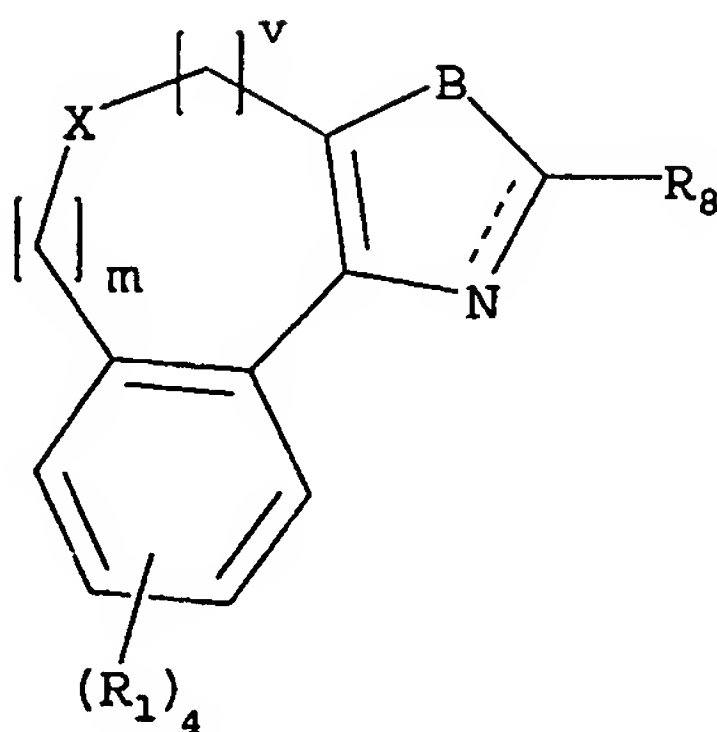
Plazzi, P.V., et al., " Heteroaryl aminoethyl and
Heteroarylthioethylimidazoles. Synthesis and H₃-Receptor
35 Affinity", Eur. J. Med. Chem. (1995) 30(11): 881-889.

- Sahu, A., and Kalra, S.P. (1993). Neuropeptidergic regulation of feeding behavior (neuropeptide Y). Trends Endocrinol. Metab. 4: 217-224.
- 5 Stanley, B. G., and Leibowitz, S. F. (1984). Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci. 35: 2635-2642.
- 10 Stanley, B. G., Magdalin, W., Seirafi, A., Nguyen, M. M., and Leibowitz, S. F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y₁ receptor mediating this peptide's effect. Peptides 13: 581-587.
- 15 Wahlestedt, C., Edvinsson, L., Ekblad, E., and Hakanson, R. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y₁ and Y₂ receptors. In: *Neuronal messengers in vascular function*, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987).
- 20 Wahlestedt, C., and Reis, D. J. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352.
- 25 Zhao, Z., et al., "Synthesis of trans-4-Alkenyloxazoles" Tetrahedron. Lett. (1991) 32(13): 1609-1612.

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What is claimed is:

1. A compound having the structure:



5

wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

10

wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

15

wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein B is O, NH or S;

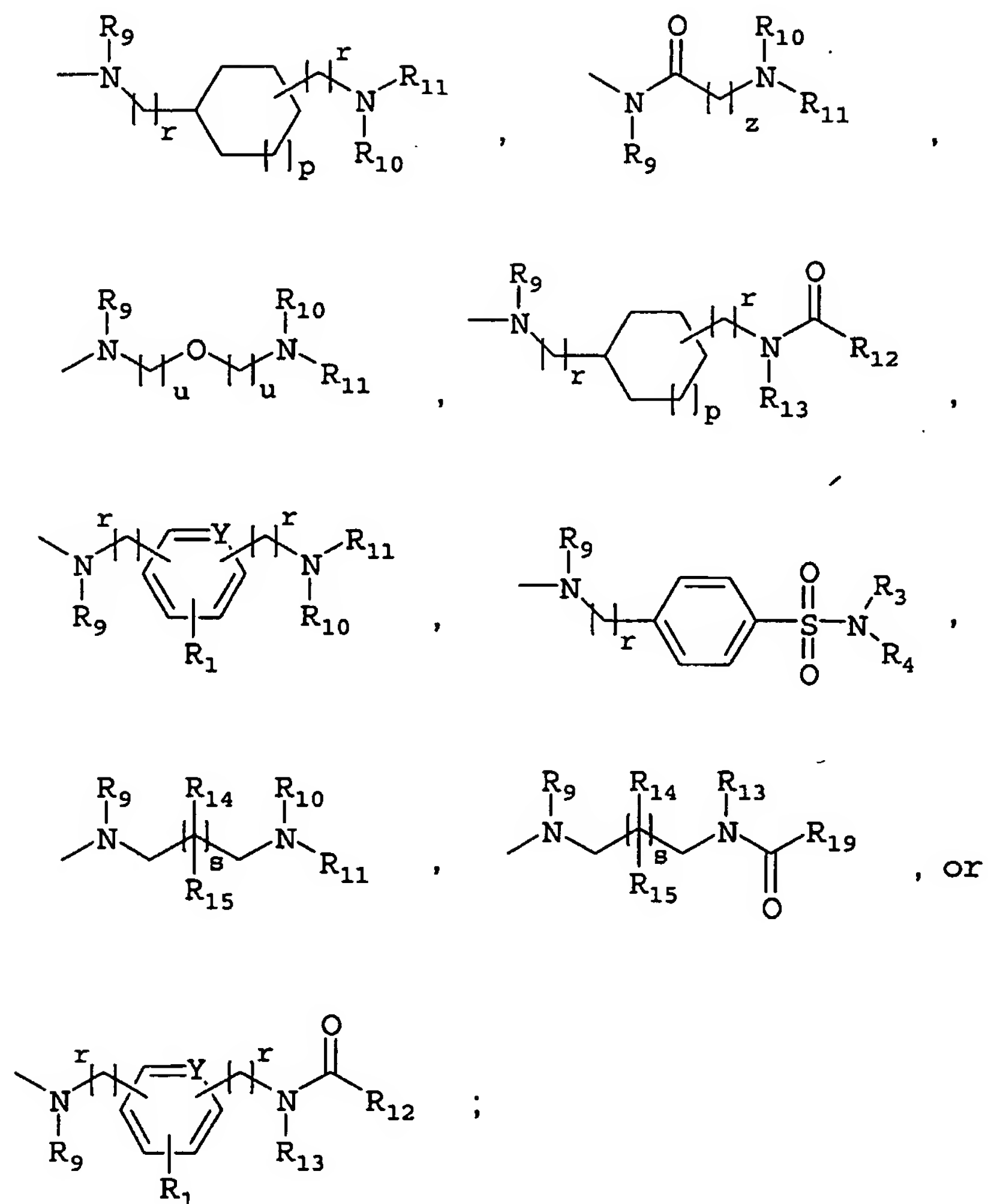
20

wherein X is CHR₅, O or NR₅;

wherein each n independently is an integer from 0 to 6 inclusive;

25

wherein R_8 is



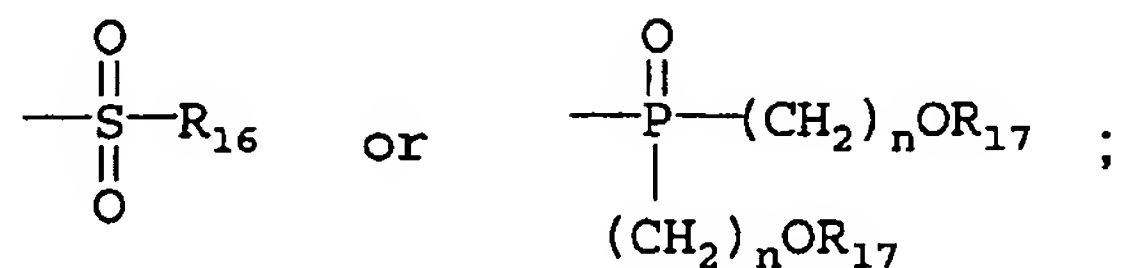
5 wherein Y is C or N;

wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

10 wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{10} is independently H; or
 straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



wherein R_{12} is H, straight chained or branched C_1 - C_7
 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X
 is O, R_{12} cannot be methyl;

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or
 branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7
 atoms may be optionally substituted with one or more
 F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained
 or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7
 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the
 phenyl or C_1 - C_6 phenylalkyl may be substituted with
 one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$,
 $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$,
 $(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight
 chained or branched C_1 - C_7 alkyl, perfluoroalkyl,
 polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which
 they are attached are pyrrolidinonyl, piperidonyl, or
 oxazolidinonyl; provided that when X is O, R_{12} and R_{13}
 cannot be oxazolidinonyl;

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wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(CH_2)_rOR_5$;

wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight

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chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

5 with the proviso that when X is O and R_8 is $NR_9(CH_2)_uO(CH_2)_uNR_{10}R_{11}$, R_{16} cannot be methyl;

10 wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, C_1 - C_6 phenylalkyl or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, -CN, -
15 NO_2 , $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

25

wherein R_4 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 -
30 C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$,

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-SO₂R₅, - (CH₂)_nCOR₇, - (CH₂)_nOR₅,
 (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅,
 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇
 alkyl, perfluoroalkyl, polyfluoroalkyl, or
 5 aminoalkyl, straight chained or branched C₂-C₇ alkenyl
 or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to
 which they are attached are 1-azetidiny, 1-
 10 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein
 the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or
 1H-azepanyl is substituted with one or more of
 F, -CN, - (CH₂)_nNR₅R₆, -SO₂R₅, - (CH₂)_nCOR₇,
 (CH₂)_nOR₅, - (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅,
 15 straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl,
 straight chained or branched C₂-C₇ alkenyl or alkynyl,
 or C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or
 heteroaryl; wherein if - (CH₂)_nNR₅R₆, - (CH₂)_nOR₅, or -
 20 (CH₂)_nNR₅COR₅ are in the 2-position, then n is not 0;
 wherein the phenyl or heteroaryl may be substituted
 with one or more of F, Cl, Br, -CN, -NO₂,
 NR₅R₆, -SO₂R₅, - (CH₂)_nCOR₇, - (CH₂)_nOR₅,
 (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅,
 25 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇
 alkyl, perfluoroalkyl, polyfluoroalkyl, or
 aminoalkyl, straight chained or branched C₂-C₇ alkenyl
 or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to
 which they are attached are morpholinyl,
 thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl,
 piperazinyl, or [1,4]diazepanyl, wherein the
 morpholinyl, thiomorpholinyl, [1,4]oxazepanyl,

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[1,4]thiazepanyl, piperaziny, or
 [1,4]diazepanyl is optionally substituted with
 straight chained or branched C_1-C_5 alkyl or $(CH_2)_tOR_5$;
 and wherein the nitrogen atom of the piperaziny or
 5 [1,4]diazepanyl ring may be optionally substituted
 with $-(CH_2)_uOR_5$; $-COR_5$; straight chained or branched
 C_1-C_5 alkyl; or phenyl; wherein the phenyl may be
 substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$,
 $-NR_5R_6$, $-(CH_2)_nOR_5$, straight chained or branched C_1-C_3
 10 alkyl, perfluoroalkyl, polyfluoroalkyl, or
 aminoalkyl;

wherein R_{17} is H, straight chained or branched C_1-C_4
 alkyl, perfluoroalkyl, or polyfluoroalkyl;

15

wherein R_{19} is $(CH_2)_nOR_5$, NR_5R_6 , phenyl, or heteroaryl,
 wherein the phenyl or heteroaryl may be substituted
 with one or more of F, Cl, Br, $-CN$, $-NO_2$, $-$
 NR_5R_6 , $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-$
 20 $(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-$
 $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight
 chained or branched C_1-C_7 alkyl, perfluoroalkyl,
 polyfluoroalkyl, or aminoalkyl, straight chained or
 branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl
 25 or cycloalkenyl;

wherein m is 0 or 1;

wherein each p independently is an integer from 0 to
 30 2 inclusive;

wherein each r independently is an integer from 0 to
 3 inclusive;

wherein each ²⁶⁴s independently is an integer
from 1 to 6 inclusive;

wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to
4 inclusive;

wherein v is 1 or 2;

with the proviso that when v is 2, m is 0;

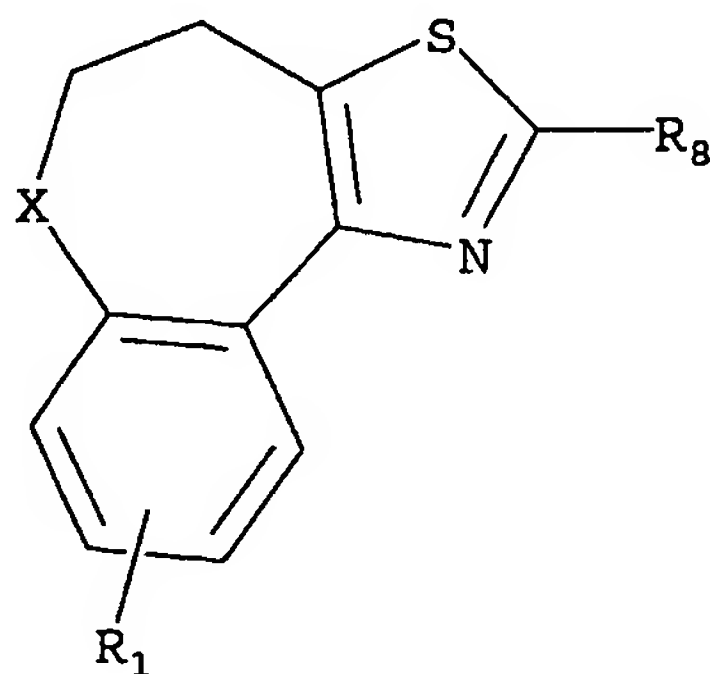
wherein z is an integer from 2 to 7;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound
comprises the (+) enantiomer.

3. The compound of claim 1, wherein the compound
comprises the (-) enantiomer.

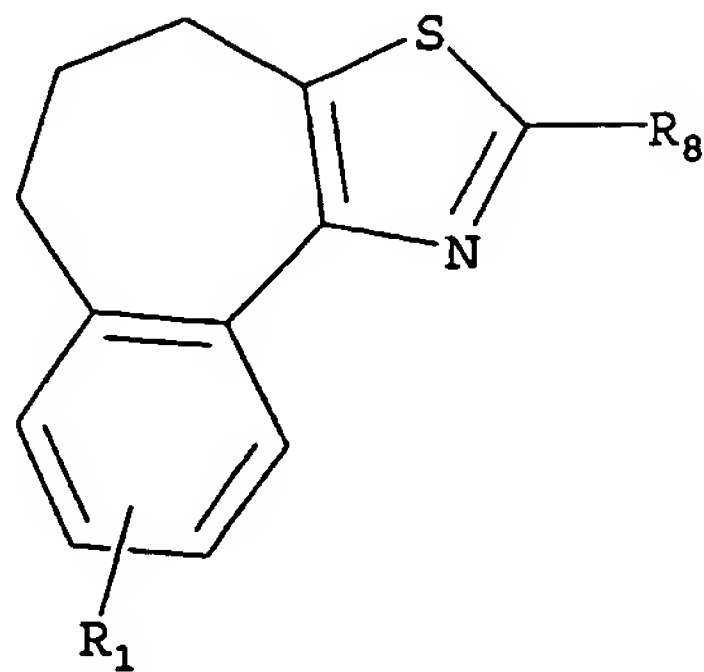
4. The compound of claim 1 having the structure:



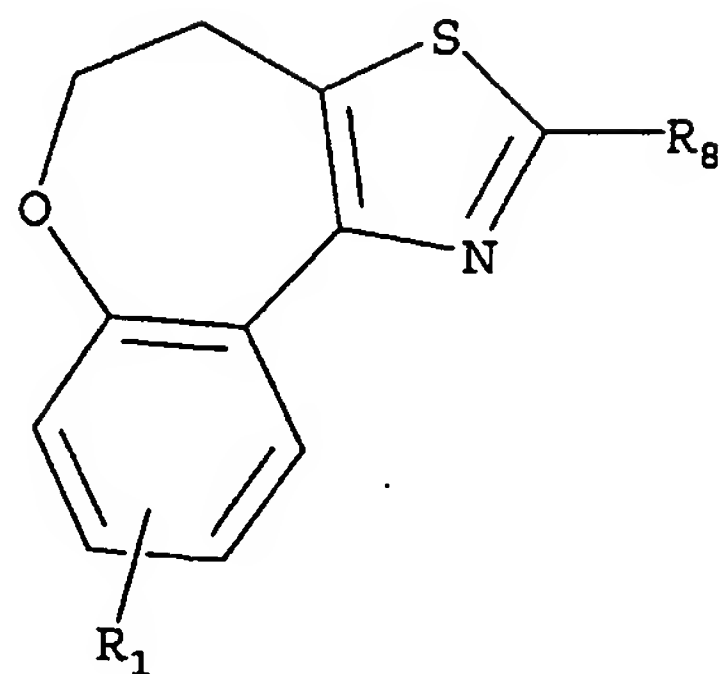
wherein X is CR₅R₆, O or NR₅.

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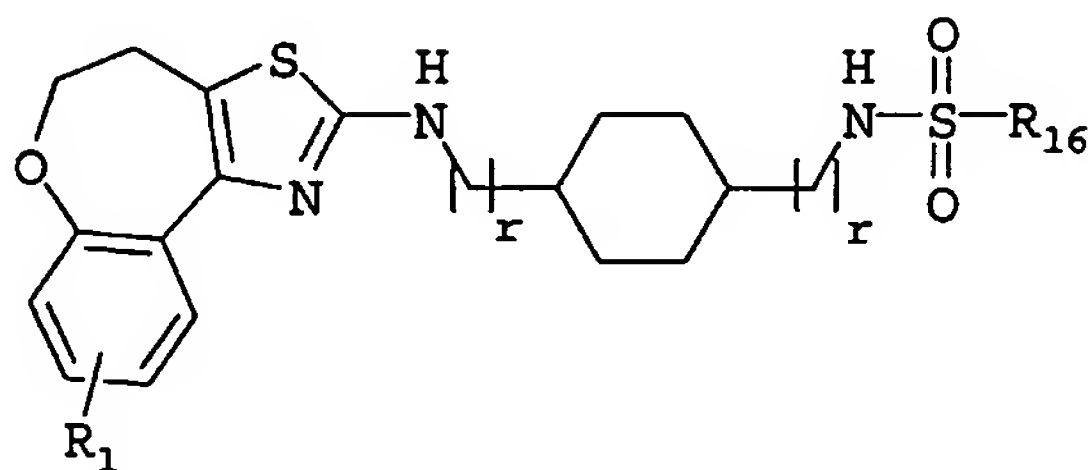
5. The compound of claim 4 having the structure:



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6. The compound of claim 4 having the structure:

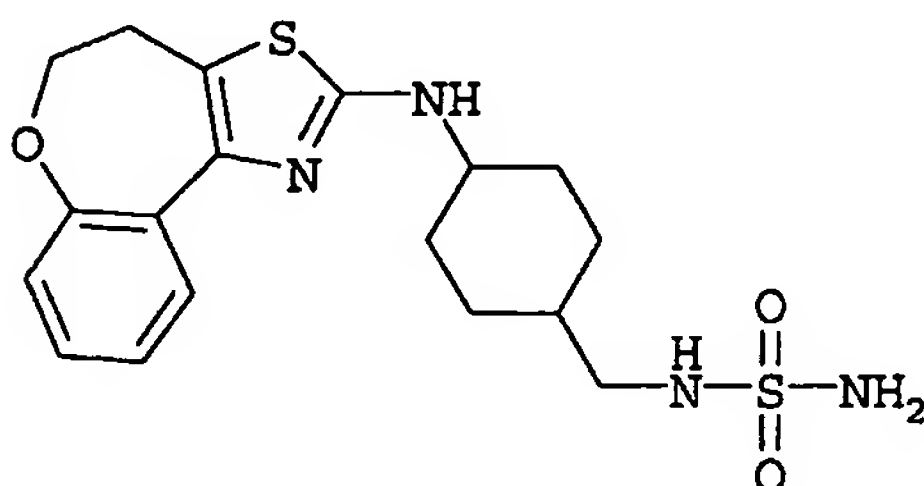
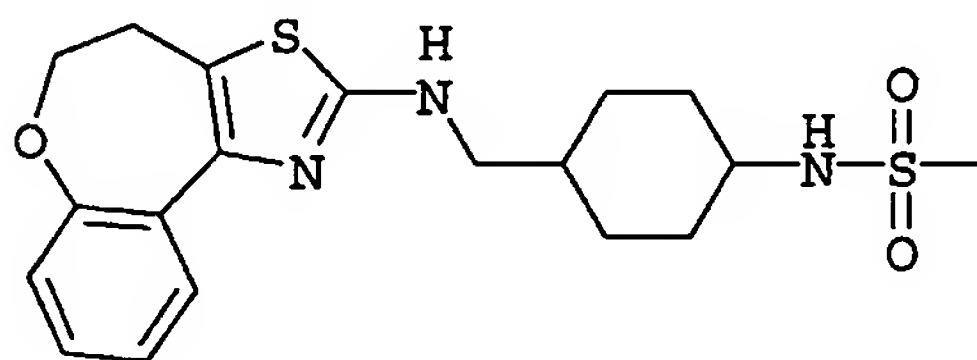
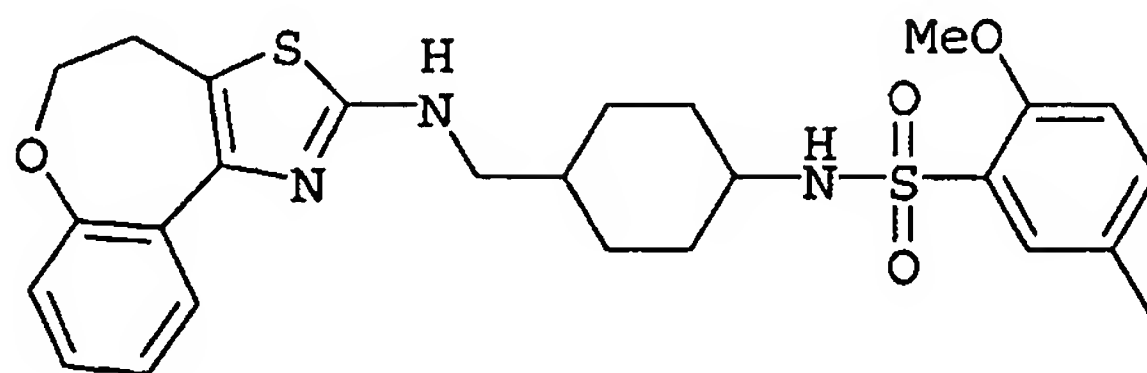


- 5 7. The compound of claim 6 having the structure:

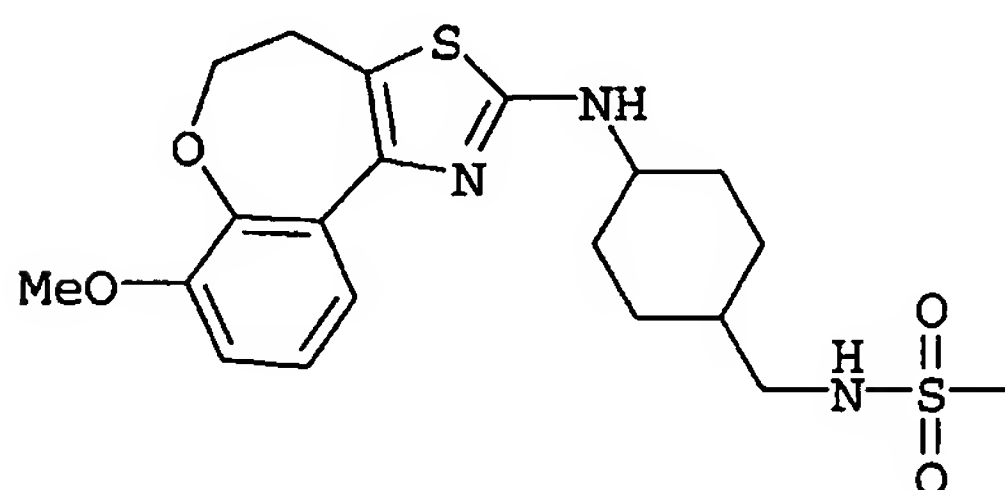


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8. The compound of claim 7 wherein the compound is selected from the group consisting of:

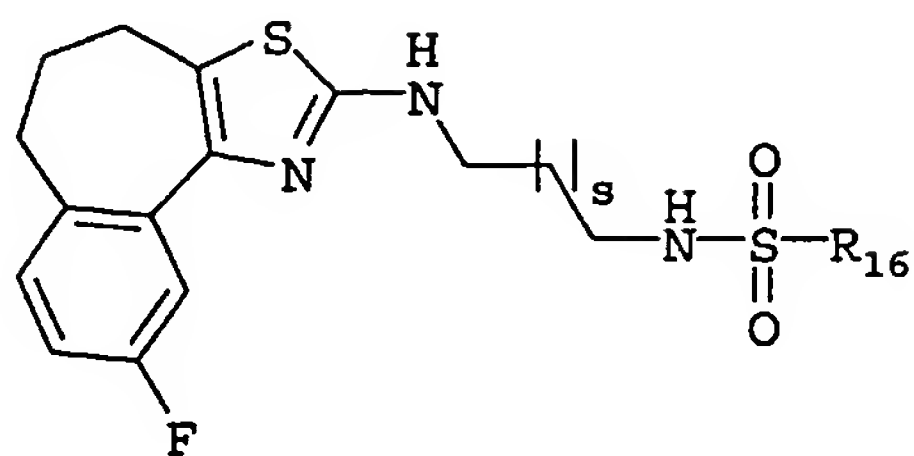


, and



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9. The compound of claim 5 having the structure:

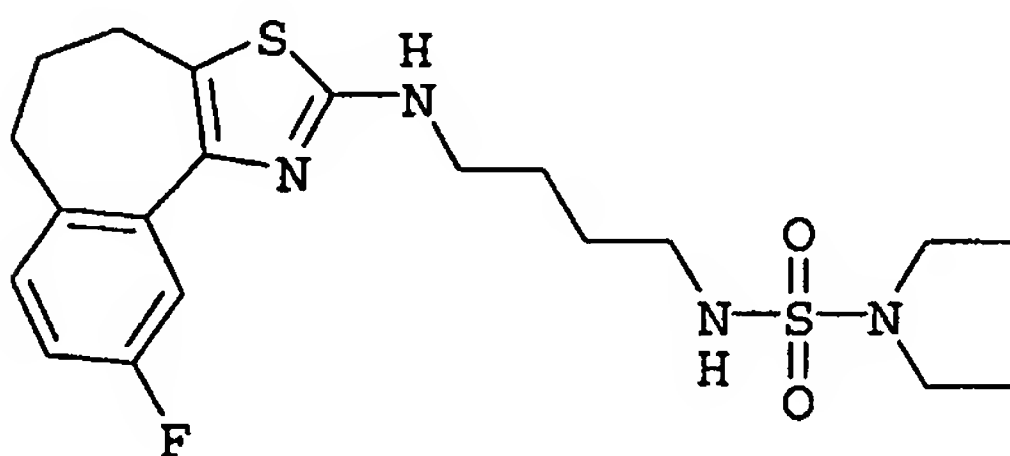
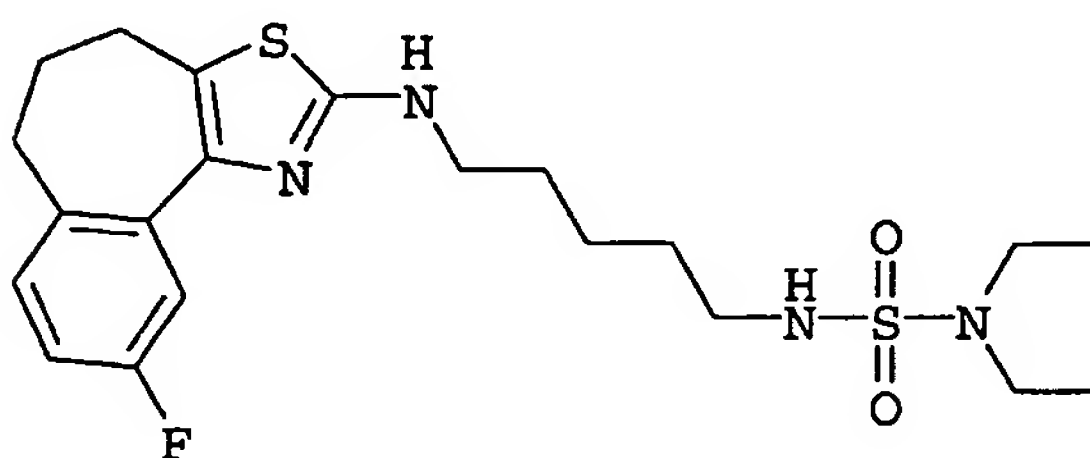
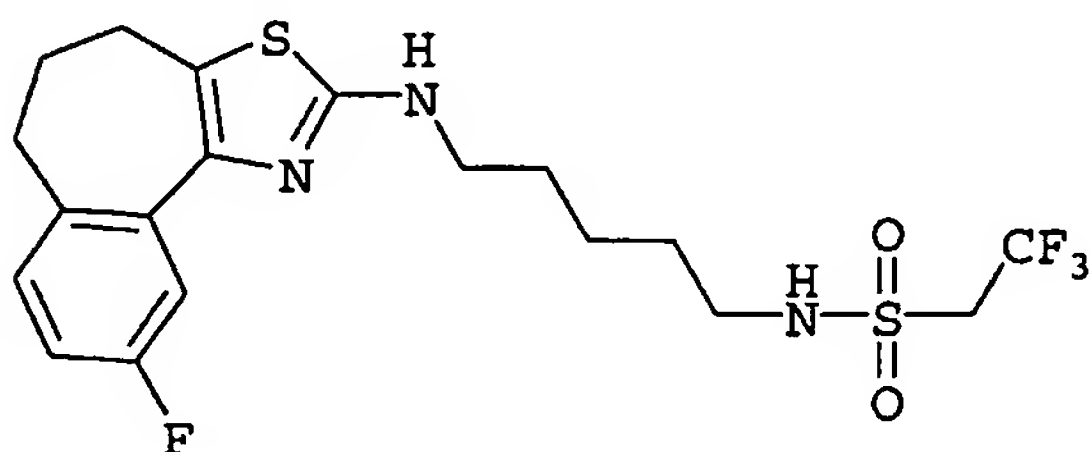
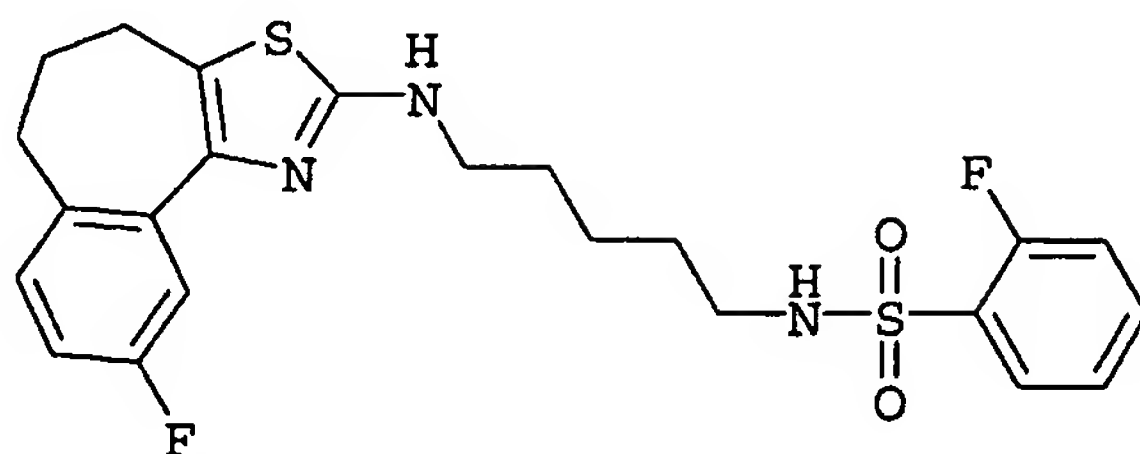


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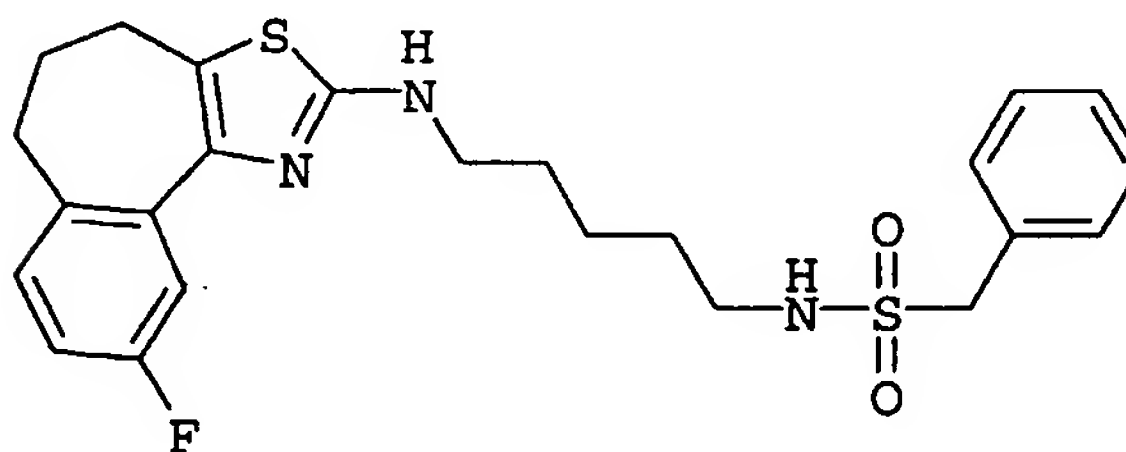
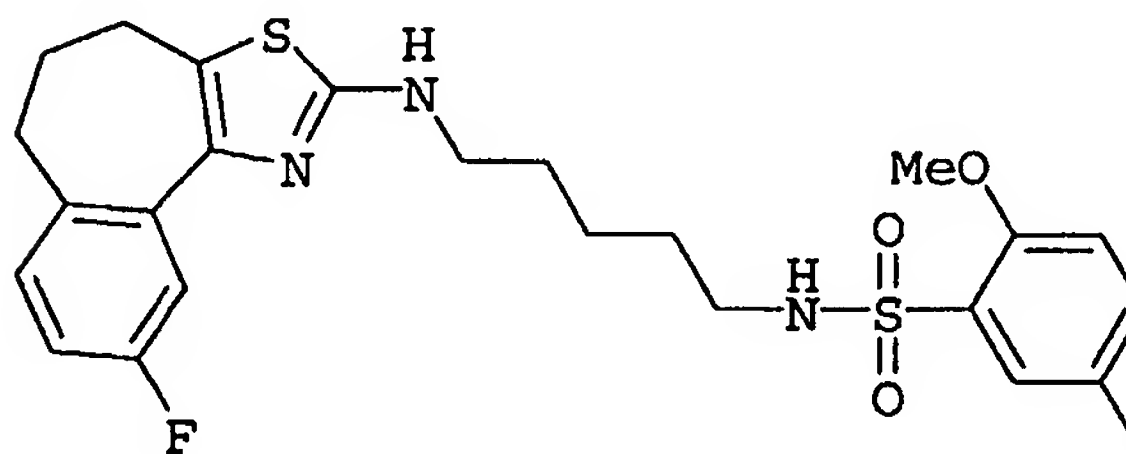
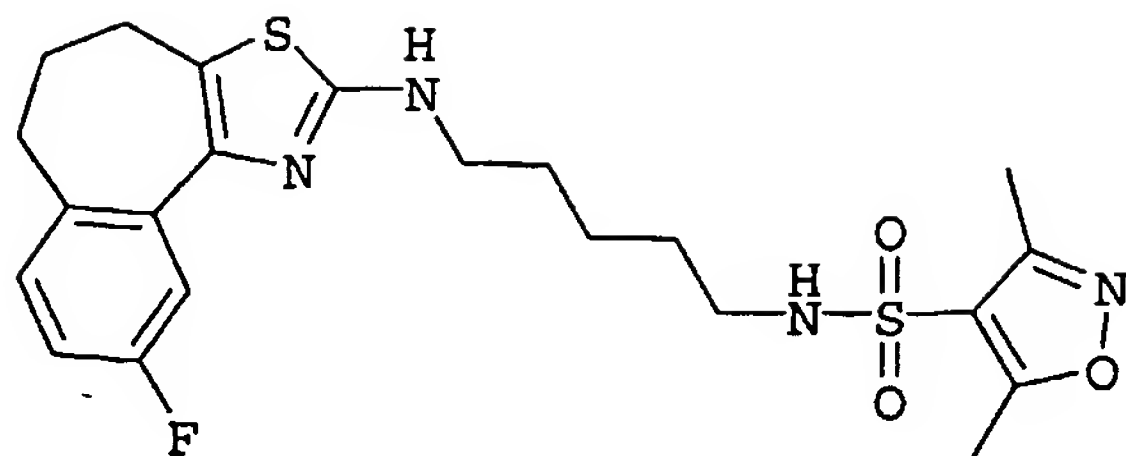
wherein s is 2, 3 or 4.

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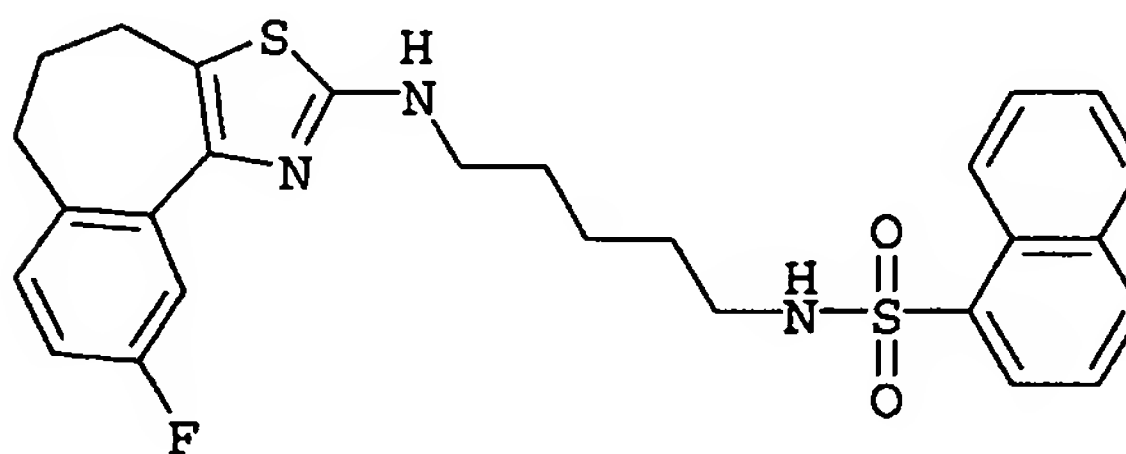
10. The compound of claim 9 selected from the group consisting of:



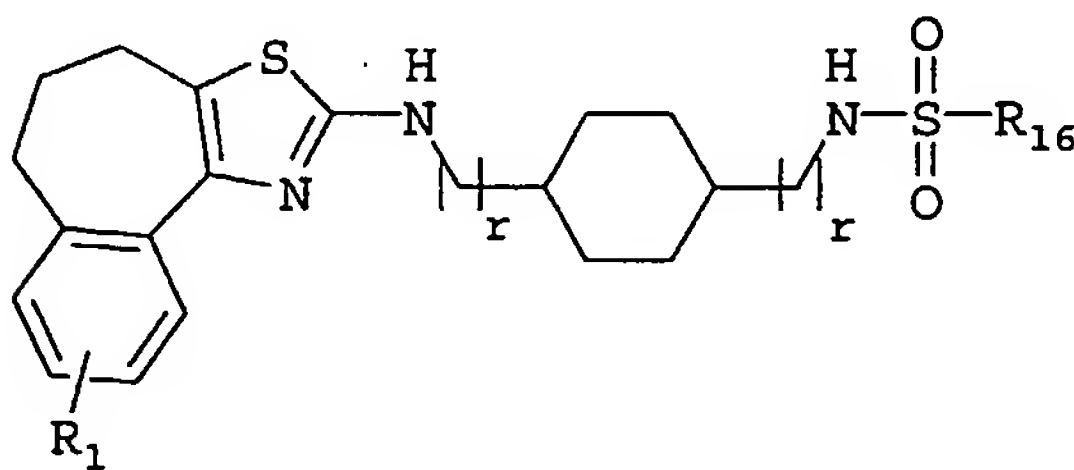
270



, and

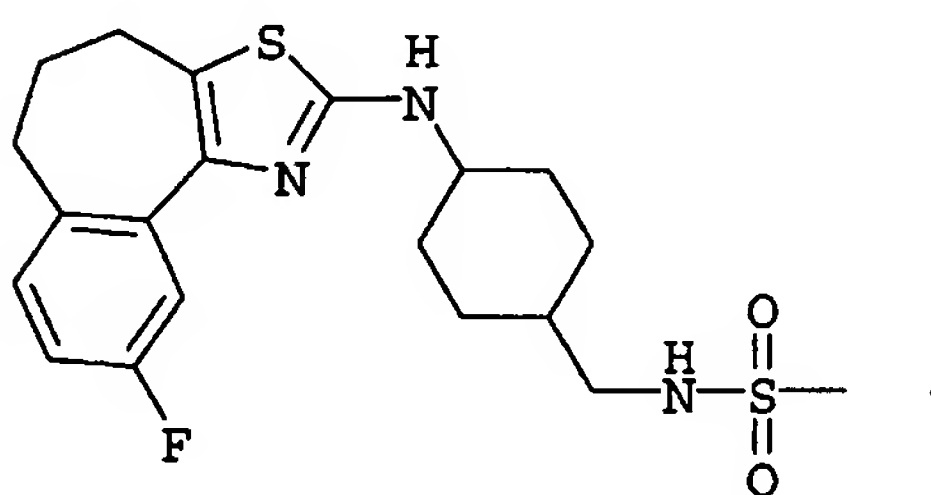
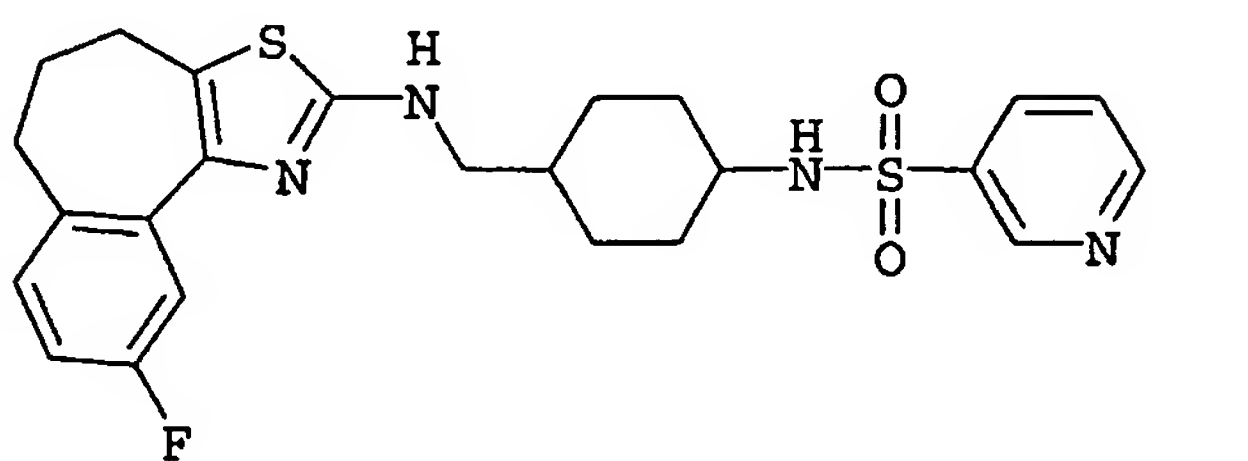
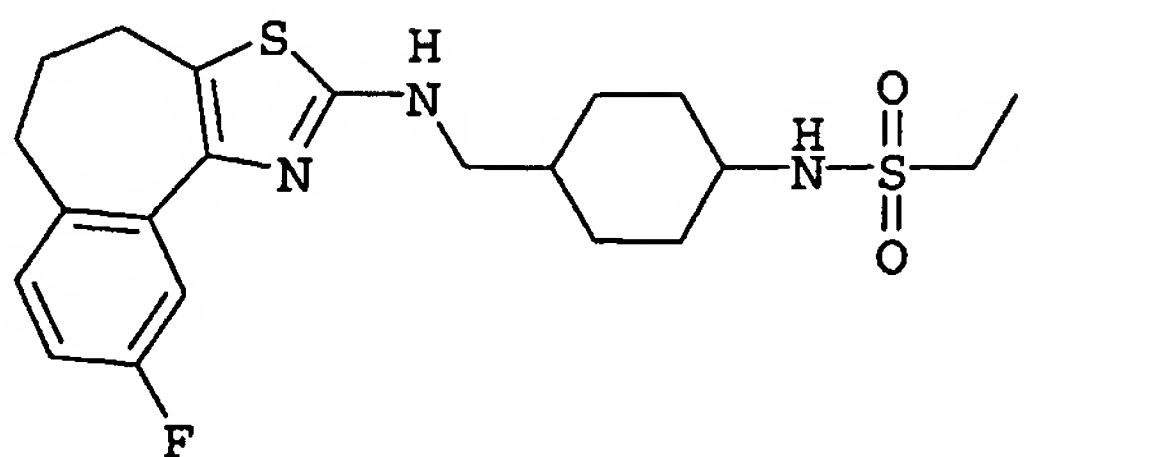


11. The compound of claim 5 having the structure:

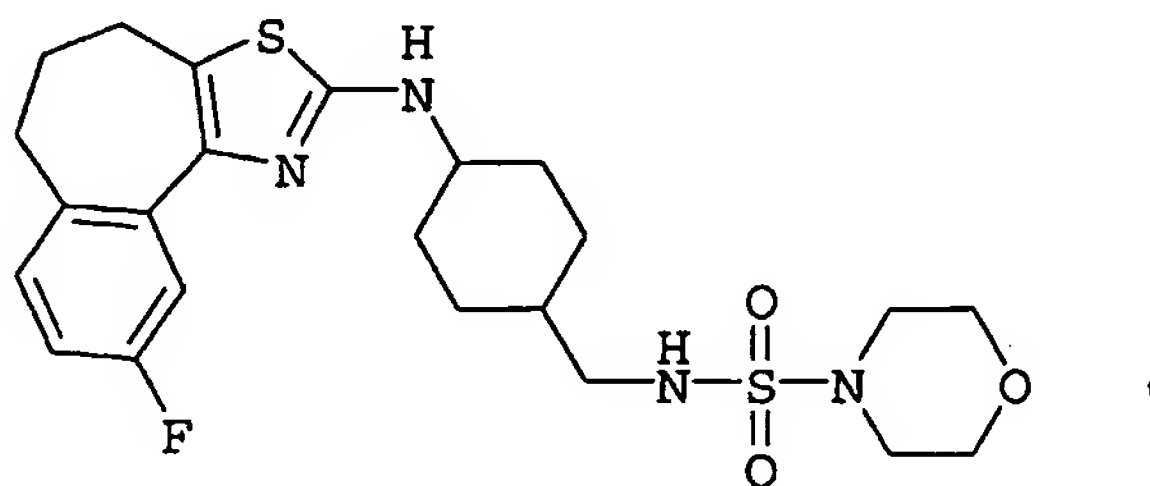
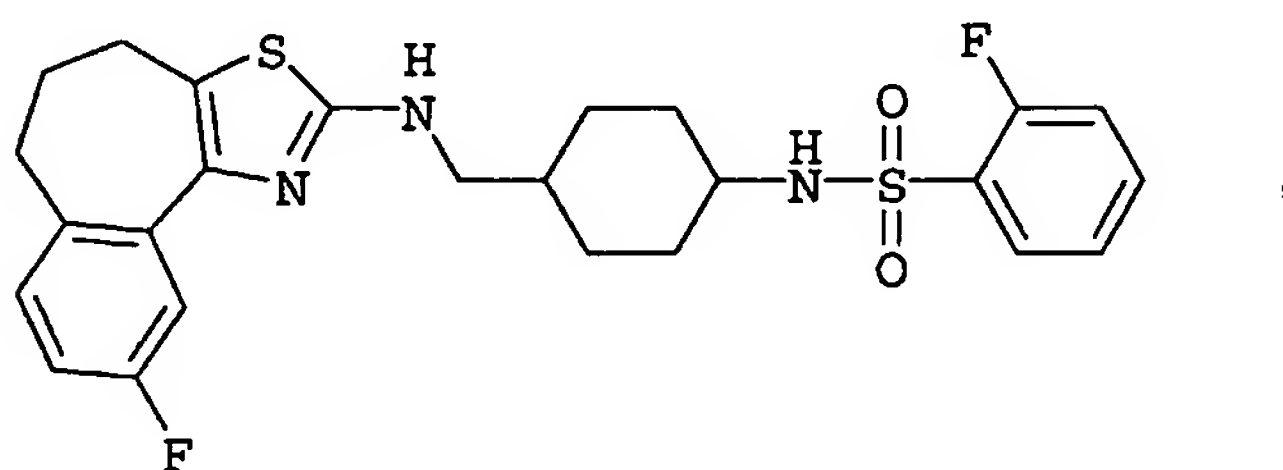
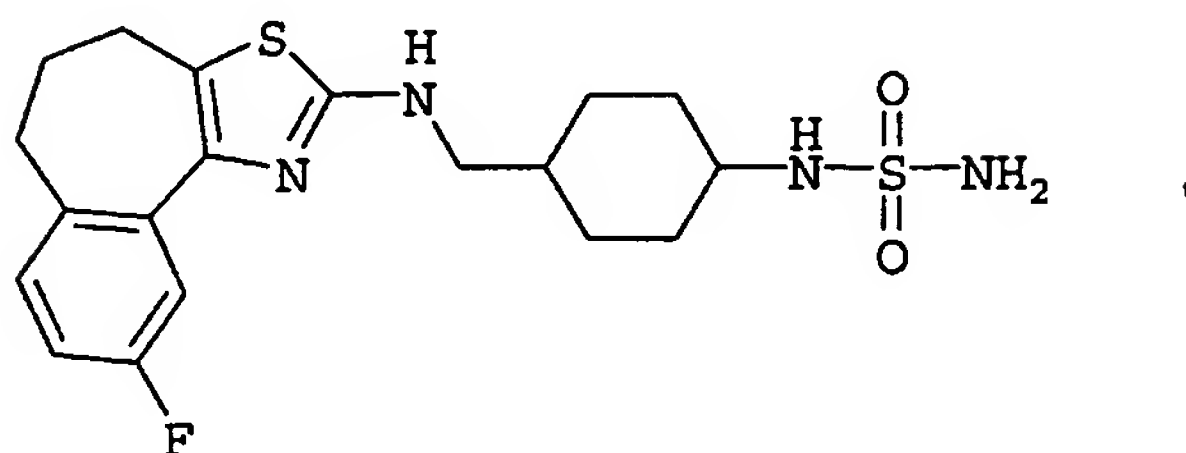
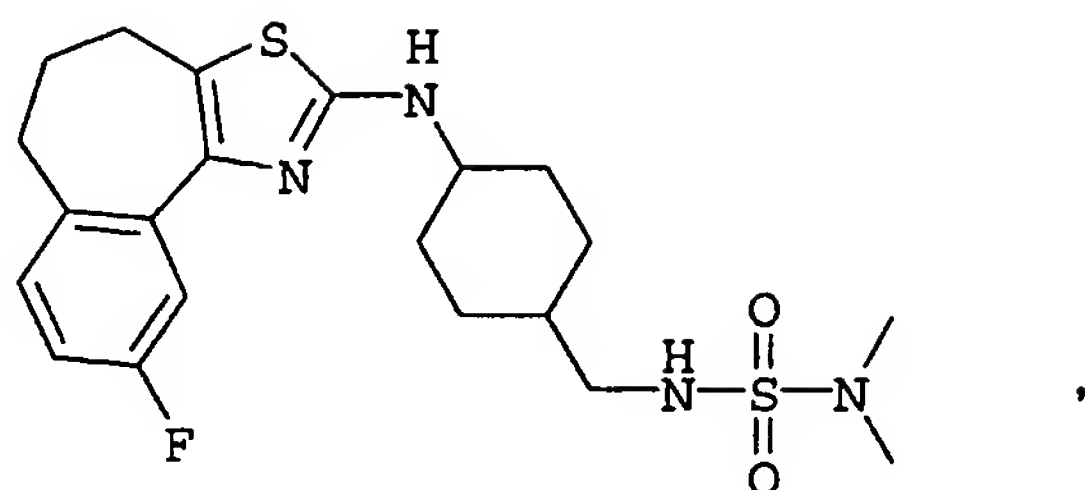


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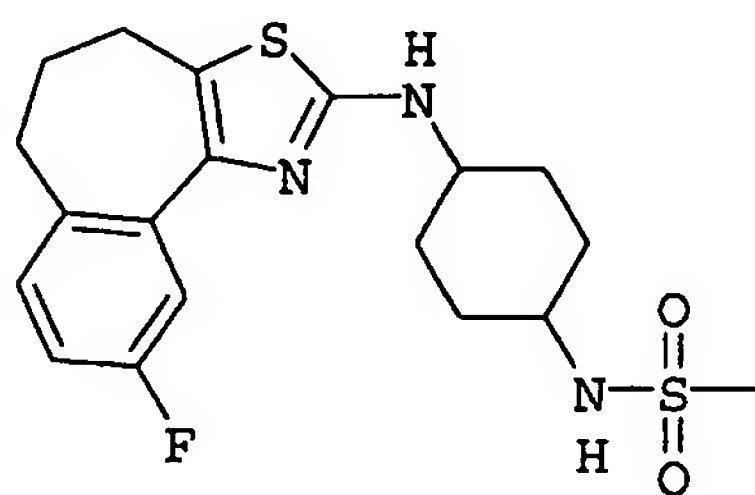
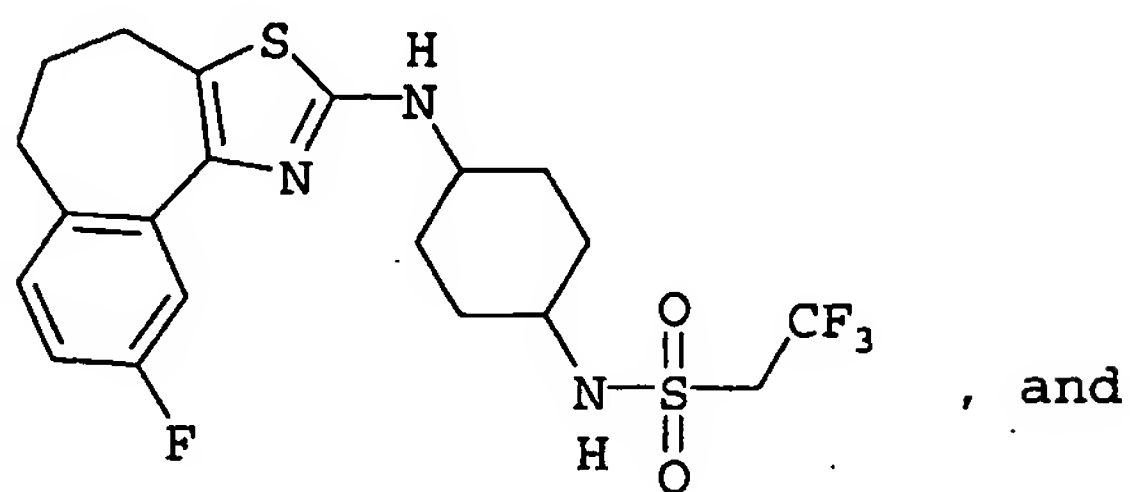
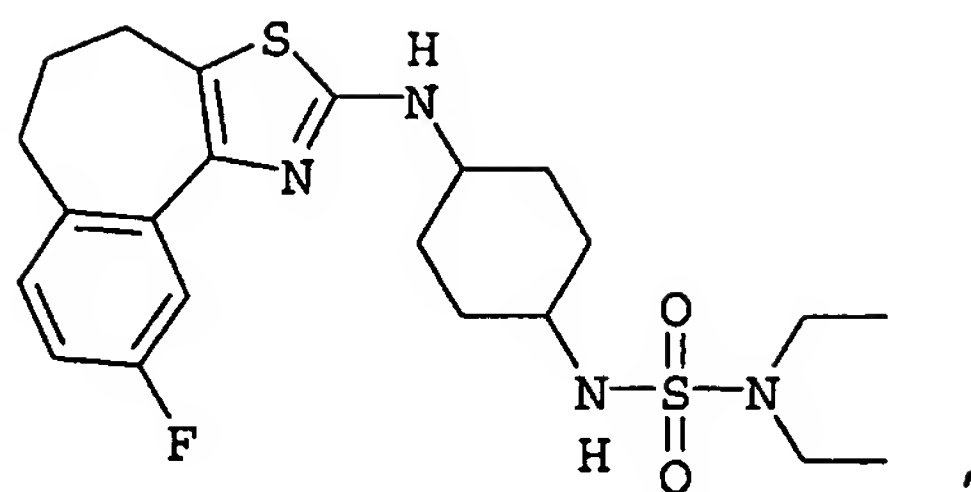
12. The compound of claim 11 selected from the group consisting of:



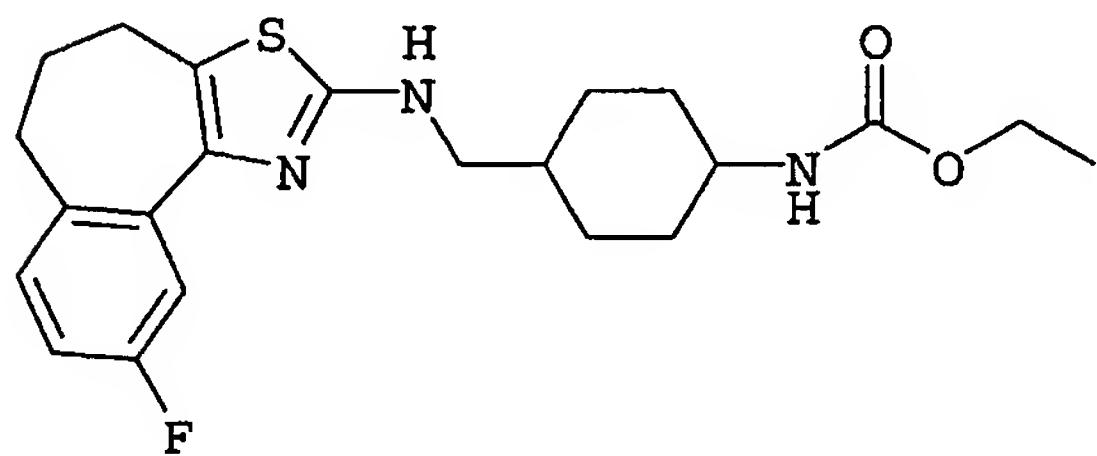
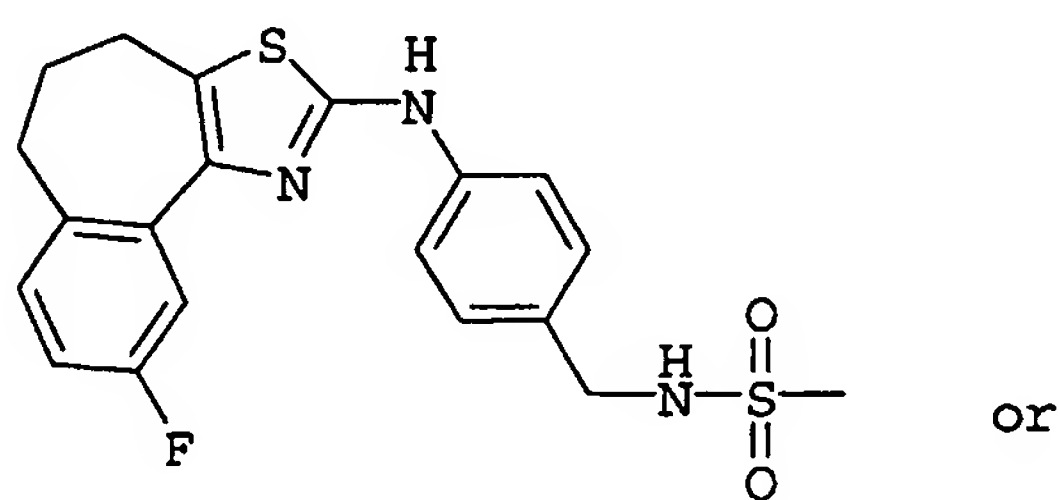
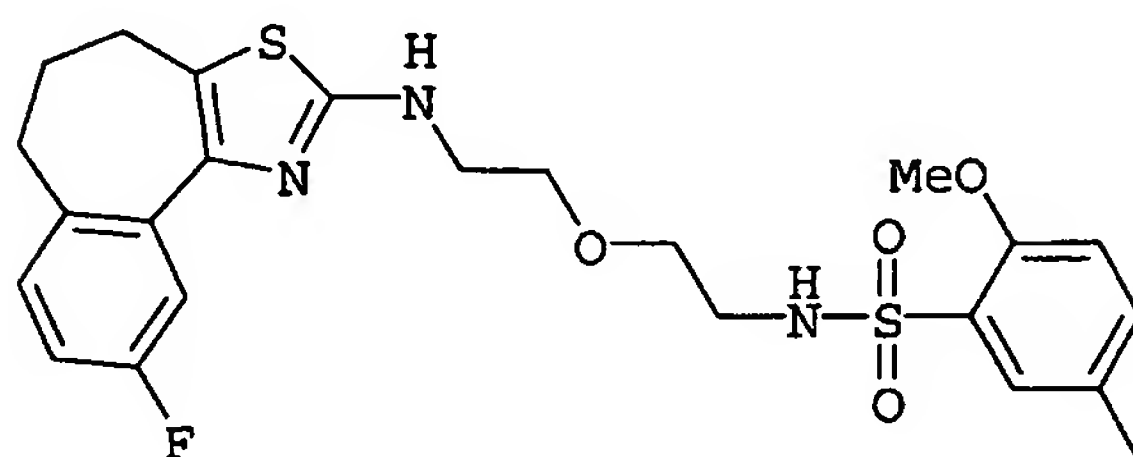
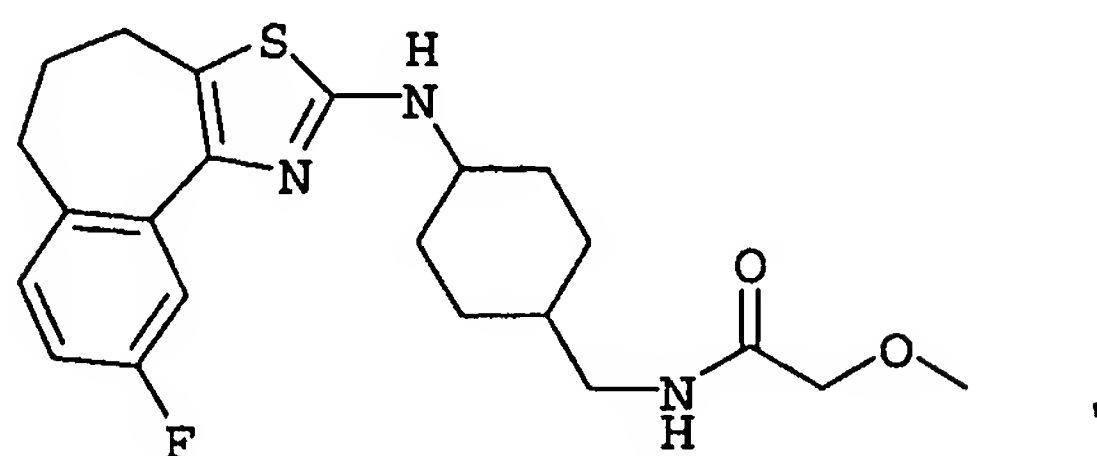
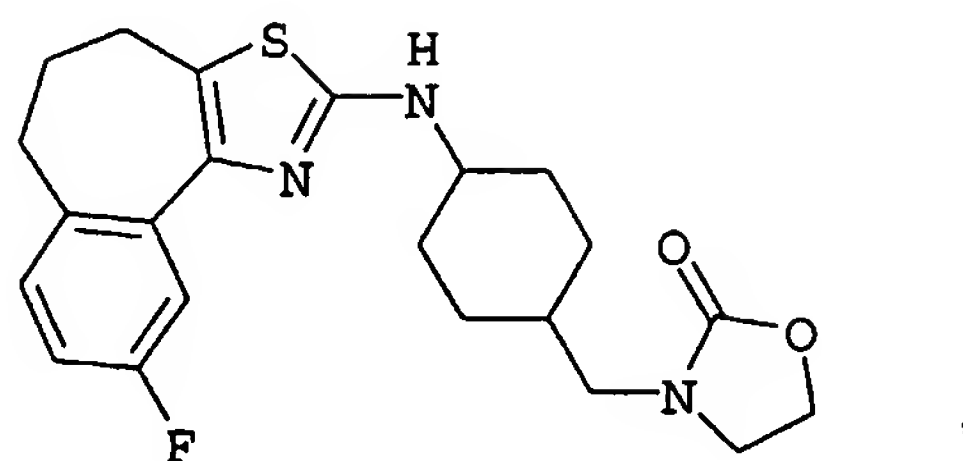
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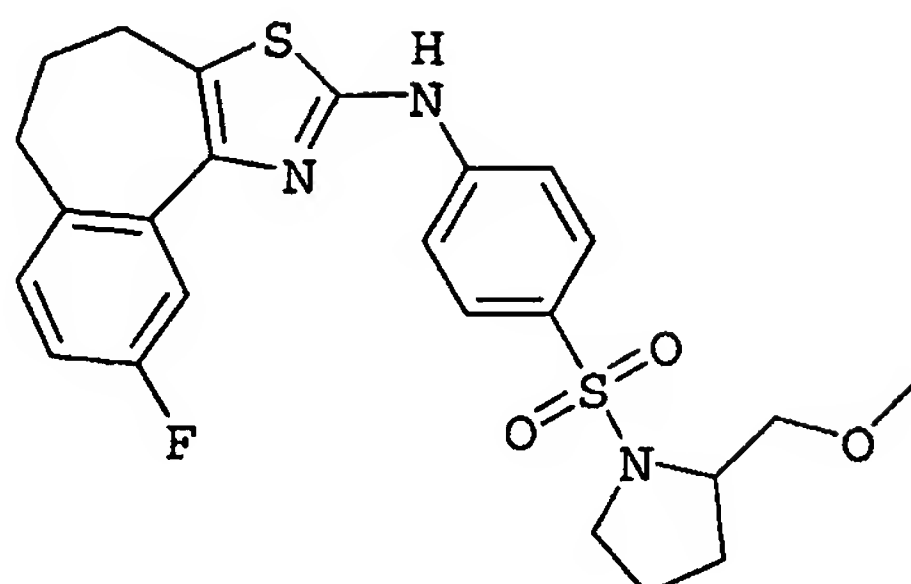


13. The compound of claim 5 having the structure:

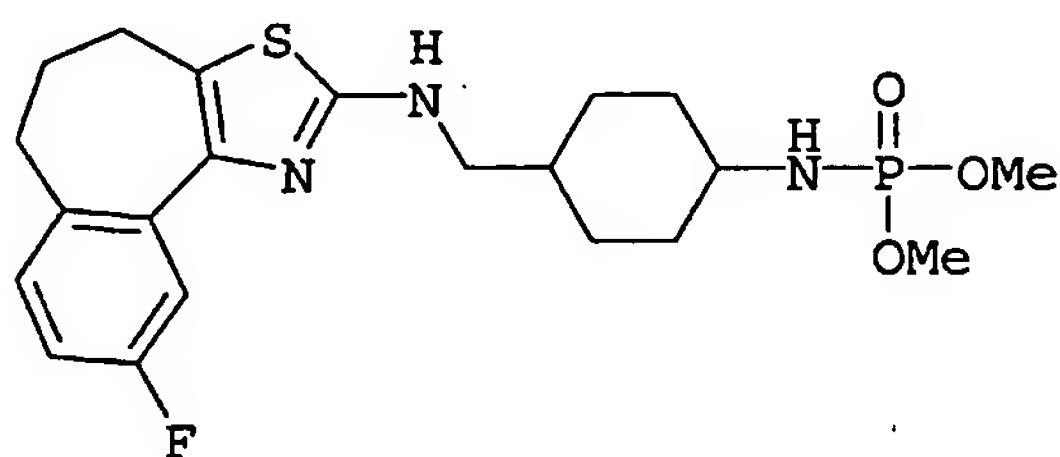


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14. The compound of claim 1 selected from the group consisting of:

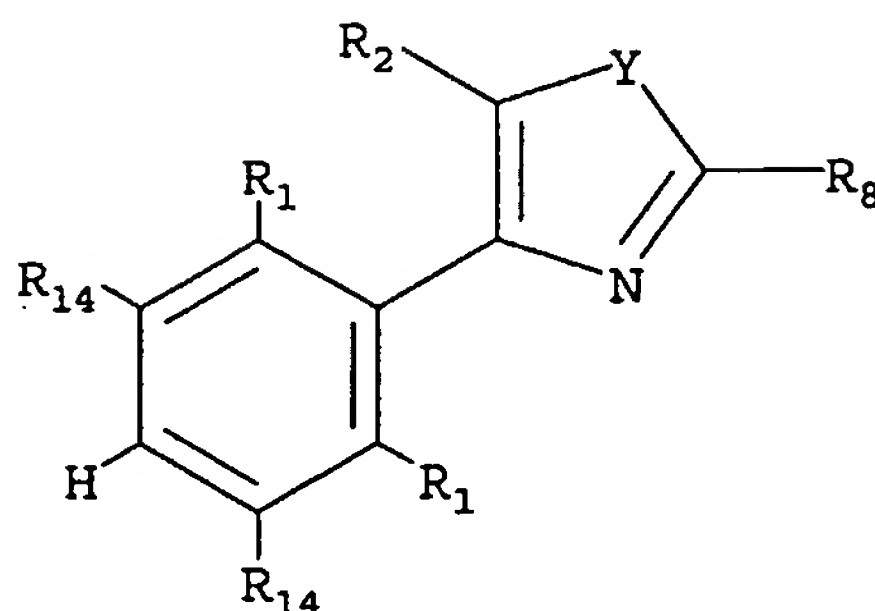


and



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15. A compound having the structure:



wherein Y is O, S or NH;

5 wherein each R_{14} independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or
 10 branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;
 15 provided that if one R_{14} is phenyl, heteroaryl or C₁-C₇ phenylalkyl, the other R_{14} is H;

wherein each R_1 independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅,
 20 -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F,
 25 Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

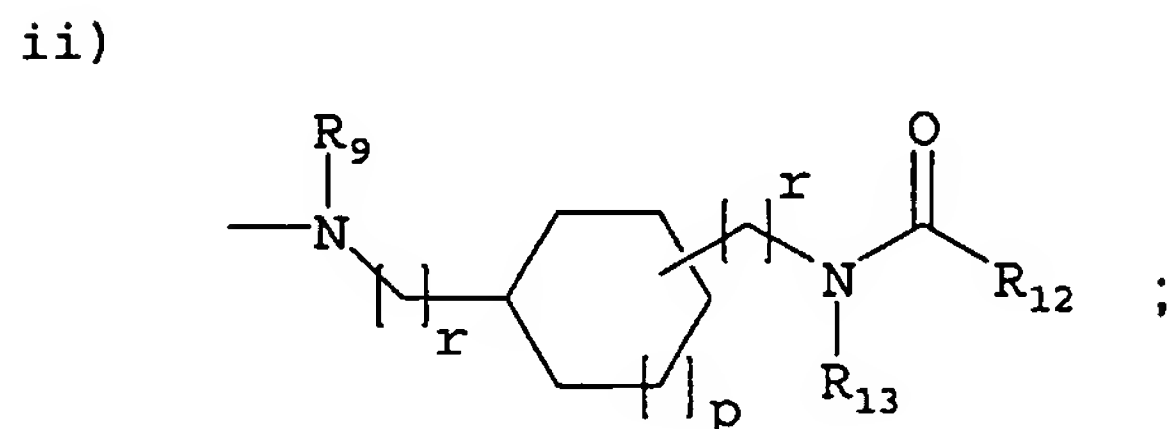
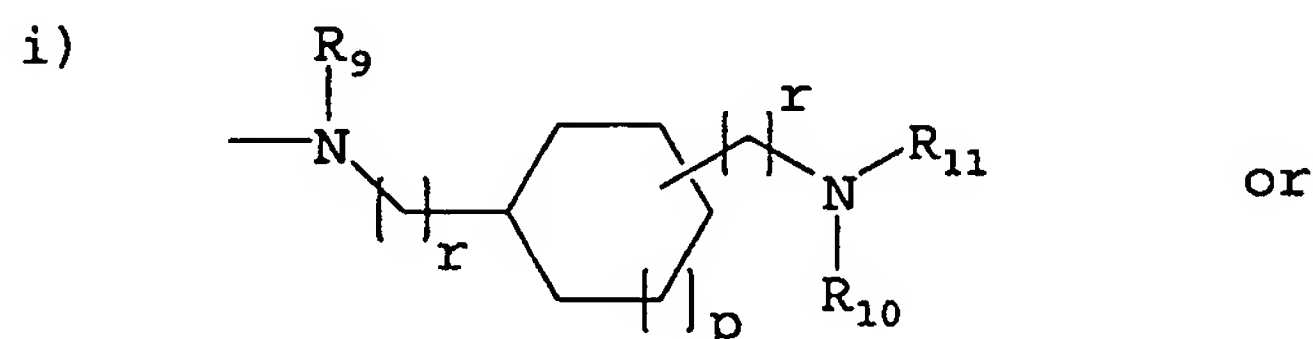
wherein R_2 is H, straight chained or branched C_1 - C_4 alkyl, $-(CH_2)_tOR_5$, phenyl optionally substituted with one or more of F, Cl, Br, $-CF_3$, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nOR_5$, or straight chained or branched C_1 - C_4 alkyl;

wherein R_5 is independently H; or straight chained or branched C_1 - C_7 alkyl;

wherein R_6 is independently H; or straight chained or branched C_1 - C_7 alkyl;

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is

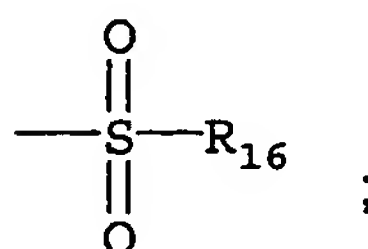


provided that R_1 or R_{14} cannot be $-OH$, when R_8 is (ii);

wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

5 wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



10

wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl; or $(\text{CH}_2)_n\text{OR}_{17}$;

15 wherein R_{13} is independently $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more
 20 F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$,
 25 $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, or straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

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or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

5 wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_{16} is NR_3R_4 , perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted
 10 straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, - NR_5R_6 , - SO_2R_5 , - $(CH_2)_nCOR_7$, -
 $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nNR_5COR_5$, -
 $(CH_2)_nCO_2R_5$, - $(CH_2)_nOCF_3$, perfluoroalkyl,
 15 polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; or phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be
 20 substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5COR_5$, - SO_2R_5 , -
 $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, -
 $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl,
 25 polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more
 30 of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , -
 $(CH_2)_nNR_5COR_5$, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, -
 $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, or straight chained or

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branched C₁-C₇ alkyl, perfluoroalkyl,
polyfluoroalkyl, or aminoalkyl;

wherein R₃ is independently H; - (CH₂)_uOR₅; -
5 (CH₂)_tCONR₅R₆; - (CH₂)_uNR₅COR₅; - (CH₂)_tCOR₇; -
(CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; straight chained or
branched C₁-C₇ alkyl; straight chained or branched C₂-
C₇ alkenyl or alkynyl; or C₃-C₇ cycloalkyl or
cycloalkenyl; or phenyl, C₁-C₆ phenylalkyl, or C₁-C₆
10 heteroarylalkyl; wherein the phenyl, C₁-C₆
phenylalkyl, or C₁-C₆ heteroarylalkyl may be
substituted with one or more of F, Cl, Br, -CN, -
NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nCOR₇, - (CH₂)_nOR₅,
- (CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅, -
15 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇
alkyl, perfluoroalkyl, polyfluoroalkyl, or
aminoalkyl, straight chained or branched C₂-C₇ alkenyl
or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; - (CH₂)_uOR₅; -
20 (CH₂)_tCONR₅R₆; - (CH₂)_uNR₅COR₅; - (CH₂)_tCOR₇; -
(CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; straight chained or
branched C₁-C₇ alkyl; straight chained or branched C₂-
C₇ alkenyl or alkynyl; or C₃-C₇ cycloalkyl or
cycloalkenyl; or phenyl or C₁-C₆ phenylalkyl; wherein
25 the phenyl or C₁-C₆ phenylalkyl may be substituted
with one or more of F, Cl, Br, -CN, -NO₂, -
NR₅R₆, -SO₂R₅, - (CH₂)_nCOR₇, - (CH₂)_nOR₅, -
(CH₂)_nCONR₅R₆, - (CH₂)_nNR₅COR₅, - (CH₂)_nCO₂R₅, -
30 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇
alkyl, perfluoroalkyl, polyfluoroalkyl, or
aminoalkyl, straight chained or branched C₂-C₇ alkenyl
or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

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or R_3 and R_4 taken together with the nitrogen atom to which they are attached are 1-azetidiny1, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny1, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, $-(CH_2)_nNR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, straight chained or branched C_1-C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, NR_5R_6 , $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1-C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl;

or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C_1-C_5 alkyl or $(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; $-COR_5$; straight chained or branched C_1-C_5 alkyl; or phenyl; wherein the phenyl may be substituted with

one or more of F, Cl, ²⁸²Br, -CN, -NO₂, -NR₅R₆ -
(CH₂)_nOR₅, straight chained or branched C₁-C₃ alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

5 wherein R₁₇ is straight chained or branched C₁-C₄
alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein each p independently is an integer from 0 to
2 inclusive;

10

wherein each r independently is an integer from 0 to
3 inclusive;

wherein t is an integer from 1 to 4 inclusive;

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wherein each u independently is an integer from 2 to
4 inclusive;

or a pharmaceutically acceptable salt thereof.

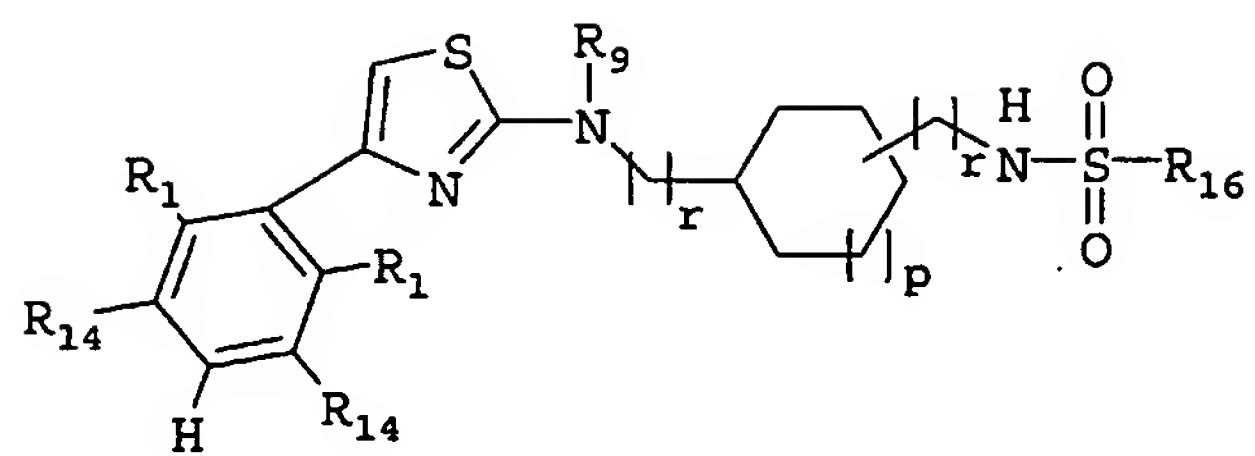
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16. The compound of claim 15, wherein the compound
comprises the (+) enantiomer.

25 17. The compound of claim 15, wherein the compound
comprises the (-) enantiomer.

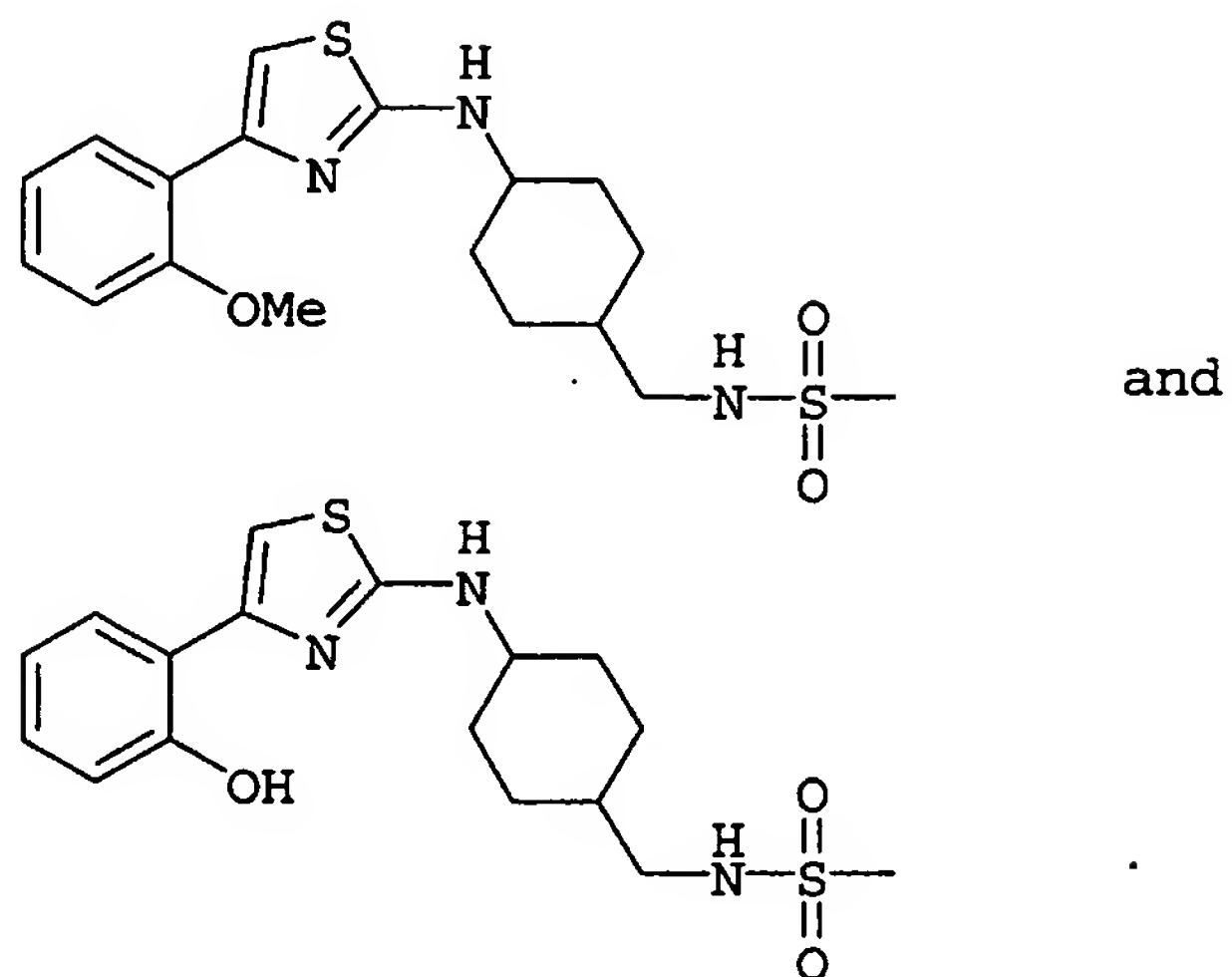
18. The compound of claim 15 having the structure:

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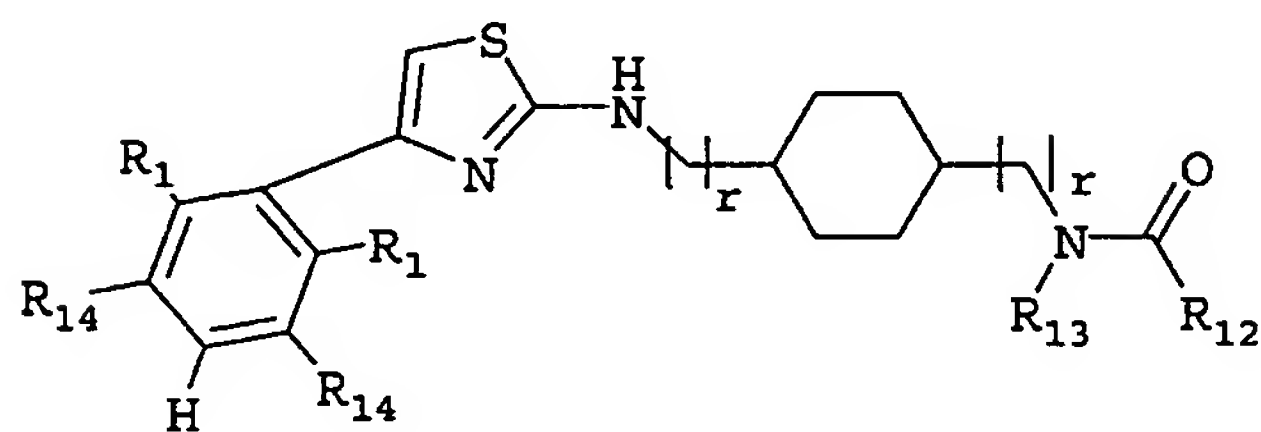
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19. The compound of claim 18 selected from the group consisting of:



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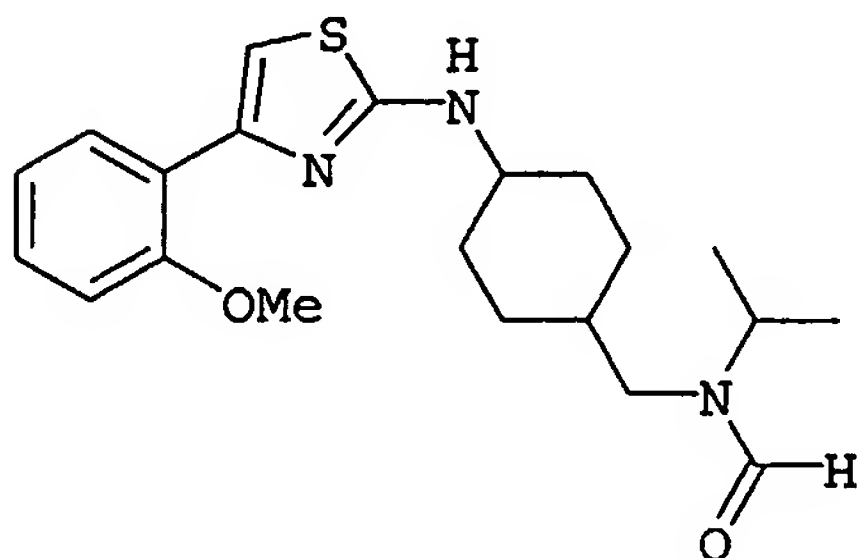
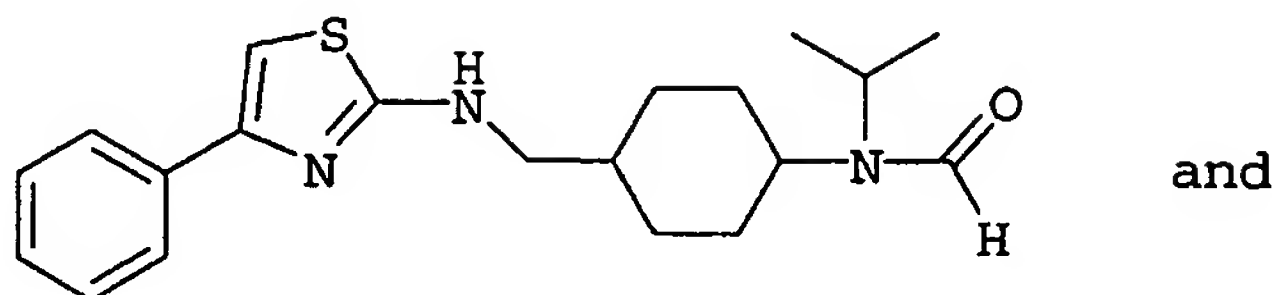
20. The compound of claim 15 having the structure:



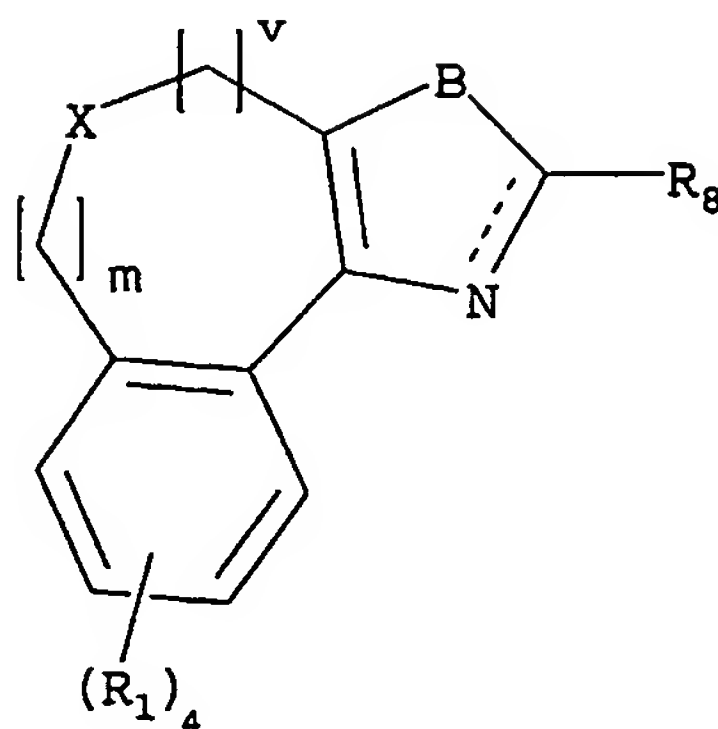
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21. The compound of claim 20 selected from the group consisting of:



22. A compound having the structure:



5 wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

10

 wherein R₅ is independently H; or straight chained or branched C₁-C₇ alkyl;

15

 wherein R₆ is independently H; or straight chained or branched C₁-C₇ alkyl;

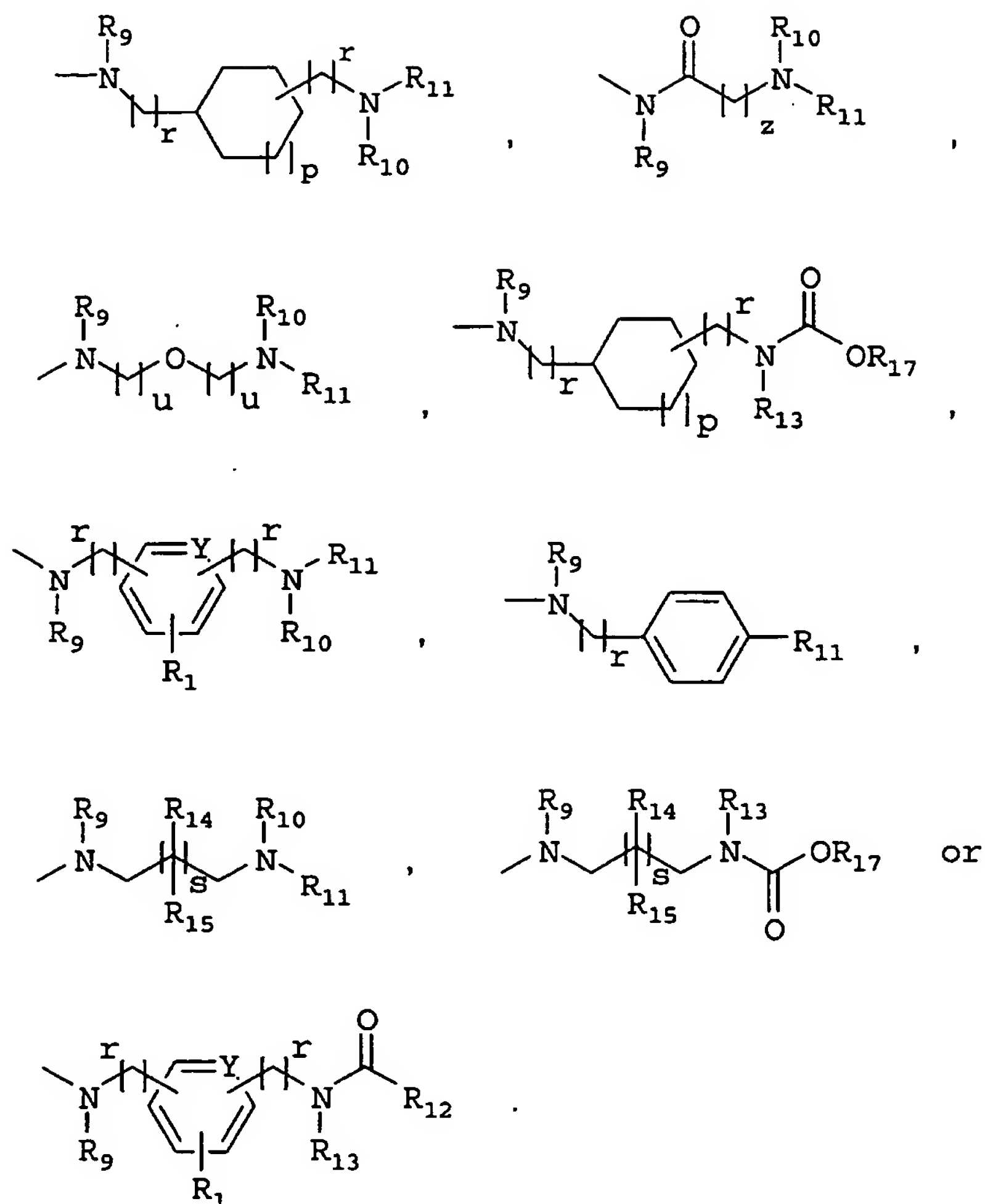
 wherein B is O, NH or S;

 wherein X is S, SO or SO₂;

20

 wherein each n independently is an integer from 0 to 6 inclusive;

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wherein R_8 is

5

wherein Y is C or N;

wherein R_7 is independently straight chained or
 10 branched C_1 - C_7 alkyl;

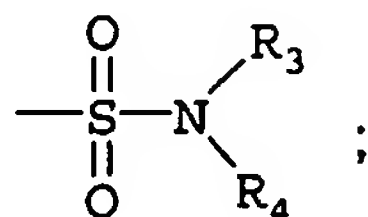
wherein R_9 is independently H; or straight chained or
 branched C_1 - C_4 alkyl;

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wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is

5



wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_n\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_n\text{OR}_{17}$;

10

wherein R_{13} is independently H; $-(\text{CH}_2)_n\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_n\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_n\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

15

20

25

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

30

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

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wherein R_{15} is H, straight chained or
branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

5

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, C_1 - C_6 phenylalkyl or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, -CN, -
10 NO_2 , $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$,
15 $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$,
 $(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl
20 or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

wherein R_4 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, - NO_2 , $-NR_5R_6$,
25 $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$,
30 $(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$,
 $(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or

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aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

5 or R₃ and R₄ taken together with the nitrogen atom to which they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of

10 F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, - (CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl,

15 or C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or heteroaryl; wherein if -(CH₂)_nNR₅R₆, -(CH₂)_nOR₅, or -(CH₂)_nNR₅COR₅ are in the 2-position, then n is not 0; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -

20 NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, - (CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl

25 or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl,

30 piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C₁-C₅ alkyl or (CH₂)_tOR₅; and wherein the

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nitrogen atom of the piperazinyl or
[1,4]diazepanyl ring may be optionally substituted
with $-(\text{CH}_2)_u\text{OR}_5$; $-\text{COR}_5$; $-\text{CO}_2\text{R}_5$; straight chained or
branched C_1 - C_5 alkyl; or phenyl; wherein the phenyl
5 may be substituted with one or more of F, Cl, Br, -
CN, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{OR}_5$, straight chained or
branched C_1 - C_3 alkyl, perfluoroalkyl, polyfluoroalkyl,
or aminoalkyl;

10 wherein R_{17} is straight chained or branched C_1 - C_4
alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein m is 0 or 1;

15 wherein each p independently is an integer from 0 to
2 inclusive;

wherein each r independently is an integer from 0 to
3 inclusive;

20 wherein each s independently is an integer from 1 to
6 inclusive;

wherein t is an integer from 1 to 4 inclusive;

25 wherein each u independently is an integer from 2 to
4 inclusive;

wherein v is 1 or 2;

30 with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

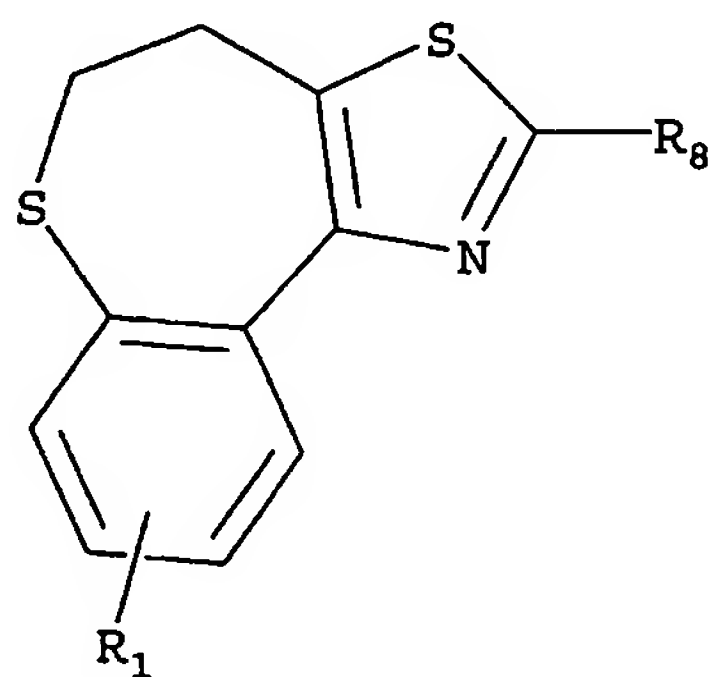
or a pharmaceutically ²⁹² acceptable salt thereof.

23. The compound of claim 22, wherein the compound comprises the (+) enantiomer.

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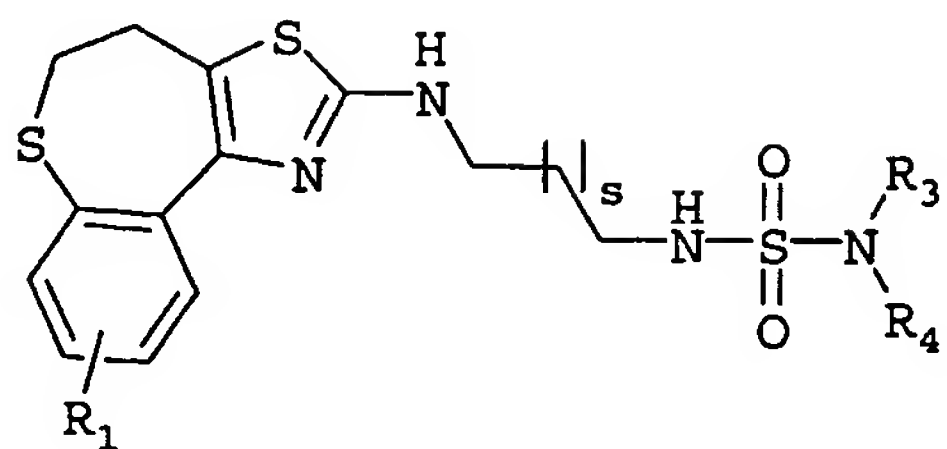
24. The compound of claim 22, wherein the compound comprises the (-) enantiomer.

25. The compound of claim 22 having the structure:



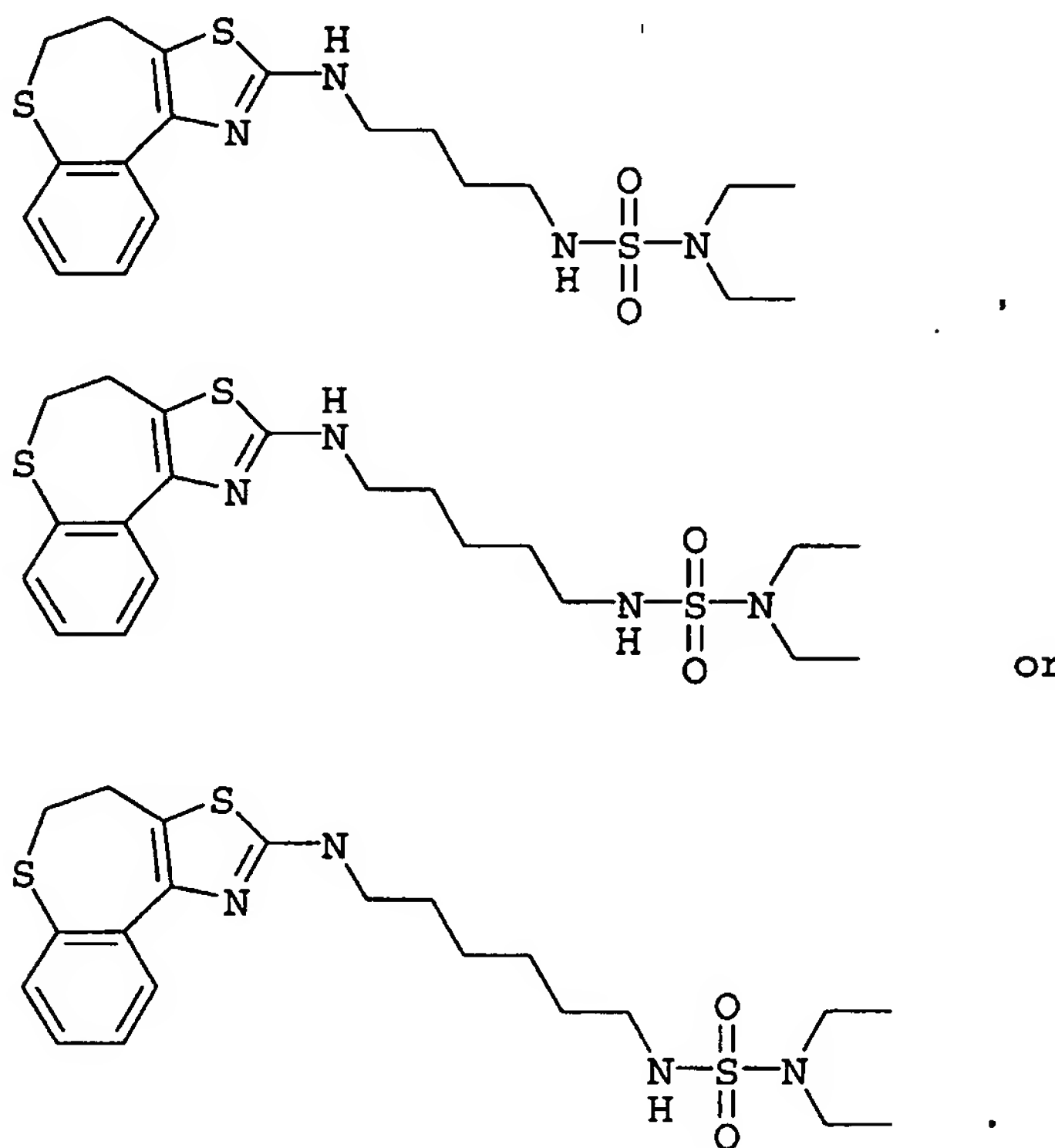
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26. The compound of claim 25 having the structure:

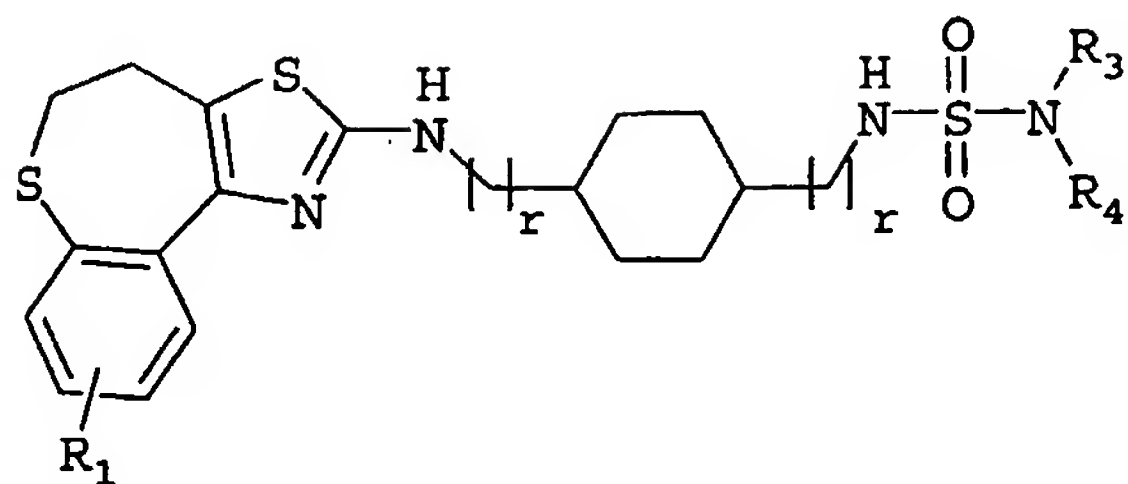


27. The compound of claim 26 having the structure:

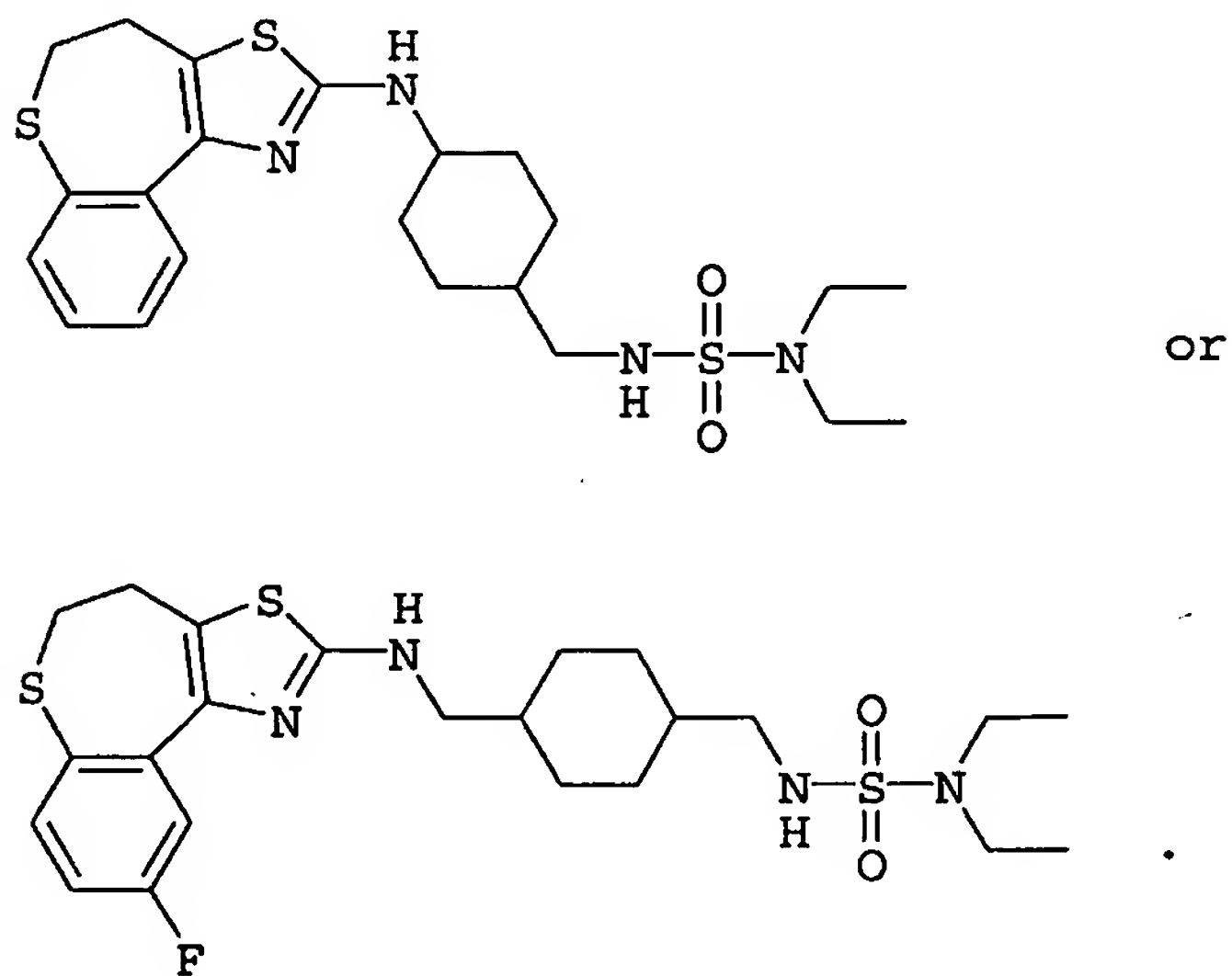
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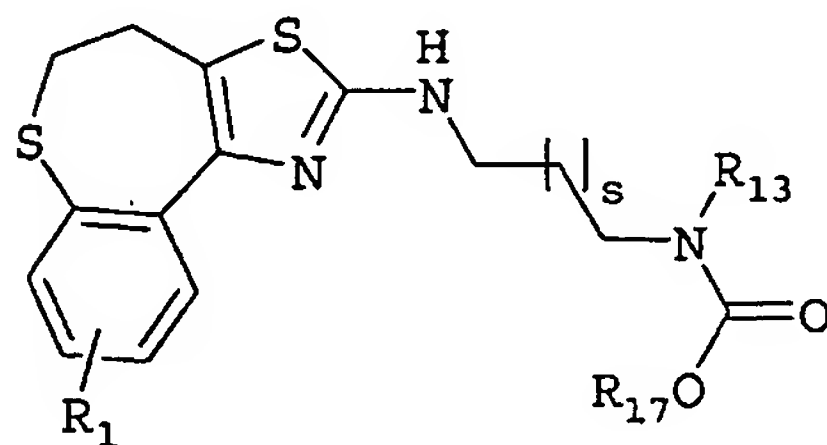
28. The compound of claim ²⁹⁴ 25 having the structure:



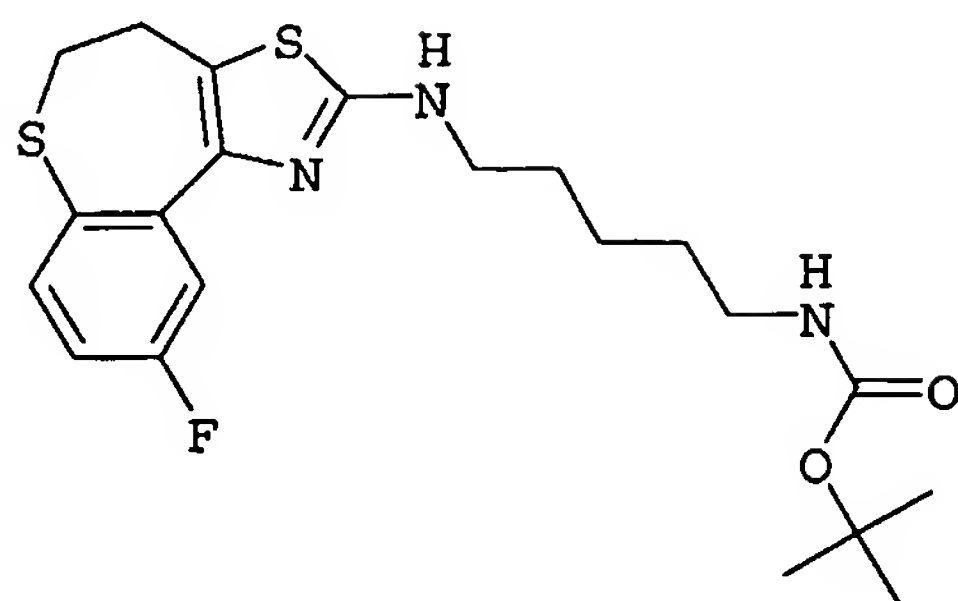
- 5 29. The compound of claim 28 having the structure:



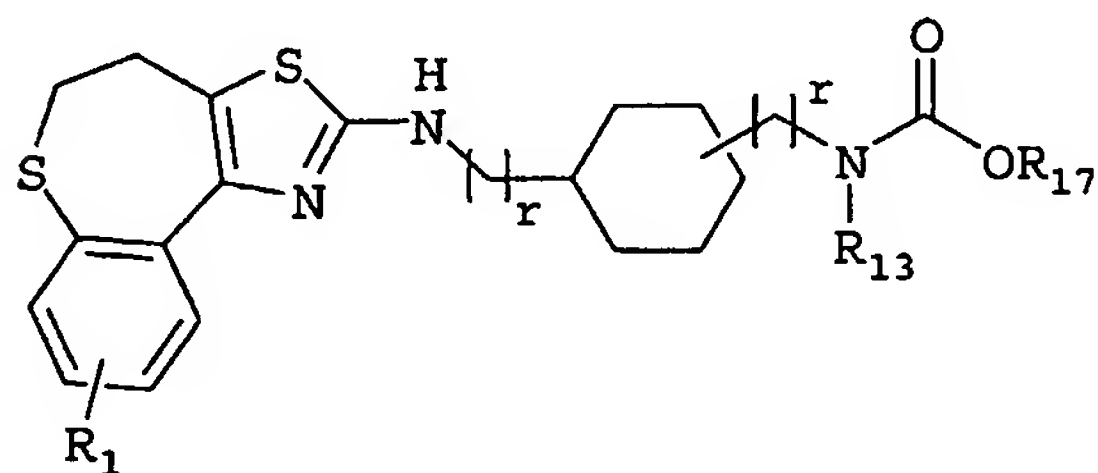
30. The compound of claim 25 having the structure:



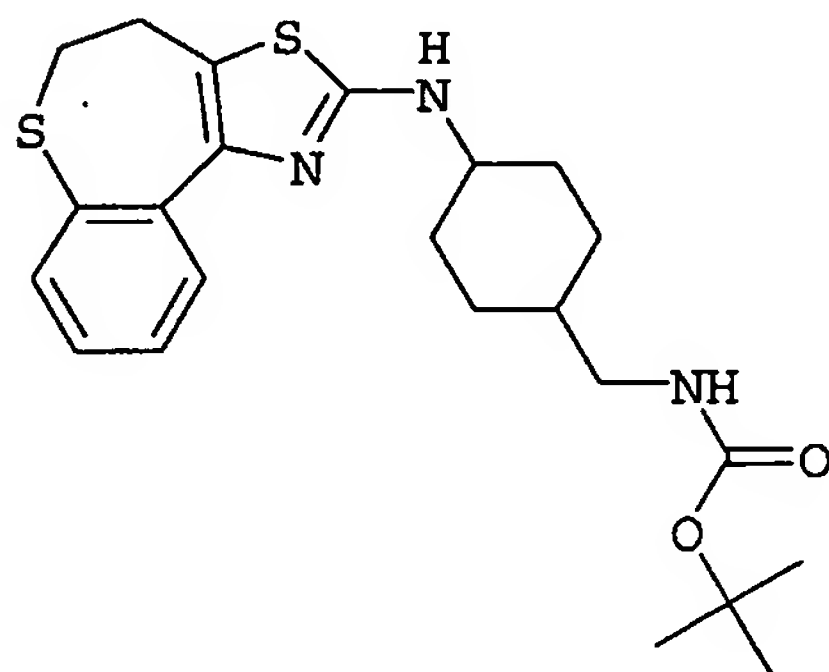
31. The compound of claim ²⁹⁵ 30 having the structure:



- 5 32. The compound of claim 25 having the structure:



33. The compound of claim 32 having the structure:



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34. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1, 15, or 22 and a pharmaceutically acceptable carrier.
- 5 35. A pharmaceutical composition of claim 34, wherein the amount of the compound is an amount from about 0.01 mg to about 800 mg.
- 10 36. A pharmaceutical composition of claim 35, wherein the amount of the compound is an amount from about 0.01 mg to about 500 mg.
- 15 37. A pharmaceutical composition of claim 36, wherein the amount of the compound is an amount from about 0.01 mg to about 250 mg.
- 20 38. A pharmaceutical composition of claim 37, wherein the amount of the compound is an amount from about 0.1 mg to about 60 mg.
- 25 39. A pharmaceutical composition of claim 38, wherein the amount of the compound is an amount from about 1 mg to about 20 mg.
40. The pharmaceutical composition of claim 34, wherein the carrier is a liquid and the composition is a solution.
- 30 41. The pharmaceutical composition of claim 34, wherein the carrier is a solid and the composition is a tablet.

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42. The pharmaceutical composition of claim 34, wherein the carrier is a gel and the composition is a suppository.
- 5 43. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1, 15, or 22 and a pharmaceutically acceptable carrier.
- 10 44. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 1, 15, or 22 and a pharmaceutically acceptable carrier.
- 15 45. Use of the chemical compound of claim 1, 15, or 22 for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human Y5 receptor.
- 20 46. Use of the compound of claim 45, wherein the abnormality is an eating disorder, obesity, bulimia nervosa, a sexual disorder, a reproductive disorder, depression, an epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, or a sleep disturbance.
- 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11004

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 277/44, 277/60; A61K 31/426, 31/428

US CL : 548/150, 151,194; 514/366, 370

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/150, 151,194; 514/366, 370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,550,138 A (SOHDA) 27 August 1996, see entire document.	1
A	US 5,166,214 A (BILLHEIMER) 24 November 1992, see entire document.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 JUNE 2000

Date of mailing of the international search report

27 JUL 2000

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